CYCLICITY AND PREMENSTRUAL SYMPTOMATOLOGY.

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ABSTRACT

This thesis reviews the major aetiological and treatment literature on premenstrual syndrome and concludes that methodological inadequacies, particularly subject selection and retrospective measurement, leaves the area in considerable disarry. Thus the first aim of the experiment, was to examine the relationship between a single interview selection proceedure and the symptom data collected over time subsequent to this interview

The second aim of the experiment was to use treatment expectations to oppose negative expectancy and so further examine the adequacy of subject selection procedures.

The third aim of the experiment was to collect sufficient prospective data to be able to use frequency domain time series analysis (spectral analysis) as an alternative to visual and non-probablistic methods of determining cyclicity

Forty two subjects who reported symptoms of premenstrual syndrome were recruited. The first interview, during the late luteal phase, was based upon the rating scales of Steiner et al.(1979). Daily mood and symptom data were collected for the next three or four menstrual cycles, at which time a second interview was held. Thirty subjects agreed to continue recording for additional treated cycles, at the conclusion of which a third interview was held.

Groups constitued on the basis of self-reported severity do vary significantly with respect to prospectively recorded mood symptoms but not with respect tp physical symptoms nor incidence. The overlapping variance between the retrospective interview ratings of severity and prospectively recorded symptoms is small but best predicted by a simple Visual

Analogue Scale rating of the previous months symptom severity.

Placebo induced treatment expectations significantly reduced incidence, premenstrual aversive mood and physical symptoms. Repeated use of the interview questionniares do not show major overlapping variance and post-treatment ratings of symptom severity do not show a significant relationship with the symptom records collected during treatment. Again the rating of the previous month on a Visual Analogue Scale was the best predictor.

The use of spectral analysis was successful in identifying both menstrual and non-menstrual cyclicity. Its use suggested three criteria for selecting subjects. They should have a menstrual length peak in both mood and physical symptom spectral density functions. These two series should show significant coherence over the range of significant menstrual period spectral density peaks. Finally these features should not be lost when placebo treatment is given.

It was concluded that the use of the above criteria and the use of both conventional and spectral density methods would be likely to reduce the confusion and uncertainty within the area and be an appropriate means of evaluating potential treatments.

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SECTION ONE - LITERATURE REVIEW

CHAPTER ONE - CLINICAL MANIFESTATIONS

1-1 INTRODUCTION

The classic definition of premenstrual syndrome (PMS) is generally acknowledged to be Frank's (1931).

> "The group of women to whom I refer especially complain of a feeling of indescribable tension from ten to seven days preceding menstruation which in most cases, continues until the time that the menstrual flow occurs. These patients complain of unrest, irritability, "like jumping out of their skins", and a desire to find relief by foolish and illconsidered actions. Their personal suffering is intense and manifests itself in many and sometimes reprehensible actions. Not only do they realize their own suffering but they feel conscience-stricken towards their husbands and families, knowing well that they are unbearable in their attitudes and reactions. Within an hour or two after the onset of the menstrual flow complete relief from both physical and mental tension occurs"(p1054).

Although clearly manifesting a sympathetic if slightly bemused outlook, this historic description of the syndrome, has precipitated a body of literature of large, and confused proportions. Almost all authors have developed a relatively idiosyncratic cluster of defining symptoms. In short there would appear almost no limits to the number of possible symptoms, particularly when one considers the linguistic licence used. In excess of 150 symptoms have been associated with the menstrual cycle (Moos, 1969). Recent reviews have reduced this list to 42 commonly reported or used symptoms (Rubinow & Roy-Bryne,1984), (Table 1).

TABLE 1-1
COMMON SYMPTOMS OF PREMENSTRUAL SYNDROME

AFFECTIVE	AUTONOMIC
sadness	nausea
anxiety	diarrhea
anger	palpitations
irritability	sweating
labile mood	
COGNITIVE	**CNS**
decreased concentration	clumsiness
indecision	seizures
paranoia	dizziness
"rejection sensitivity"	vertigo
suicidal ideation	paresthesia
	tremors
PAIN	**FLUID/ELECTROLYTE**
headache	bloating
breast tenderness	weight gain
joint and muscle pain	oliguria
	edema
NEUROVEGETATIVE	**DERMATOLOGICAL**
insomnia	acne
hypersomnia	greasy hair
anorexia	dry hair
craving for certain foods	
fatigue	**BEHAVIOURAL**
lethagy	decreased motivation
agitation	poor impulse control
libido change	decreased efficiency
	social isolation

note. From "Premenstrual Syndromes : Overview From a Methodologic Perspective" by D. R. Rubinow and P. Roy-Bryne, 1984, American Journal of Psychiatry, 141, P170.

The adequacy with which authors report their diagnostic criteria, shows similar variation and vagueness. For example some authors merely state that subjects had PMS without describing it further (Dalton, 1984), while others at least provide some diagnostic information, even if the outcome might seem to refer to another orthogonal condition (Barr, 1984)

A recent trend is to identify a cyclic state rather than symptoms. This is commented on with respect to its association with the onset of menstruation (Osmun, Steiner, & Haskett, 1983). To this extent there would seem to be a consensus that PMS is a cyclical disorder, manifested by a

considerable variety of both physical and psychological symptoms, that begins around ten days prior to menstruation and is resolved with the onset of bleeding (Reid & Yen, 1983)

Two critical dimensions exist for PMS. Firstly symptomatic expression, and secondly the temporal constraints with respect to the menstrual cycle. It is proposed to examine recent literature separately for these two issues.

1-2 SYMPTOMATIC EXPRESSION

Moos (1968; 1969), made one of the first attempts to structure this literature. The resulting 47 item Menstrual Distress Questionnaire (MDQ), contains eight symptom clusters. These were labelled pain, concentration, behavioural change, autonomic reactions, water retention, negative affect, arousal, and control.

The majority of these items relate to somatic changes with psychological symptoms being contained within only two categories. This reflects a bias towards total menstrual cycle phenomena, and thus dilutes its effectivness as a standardised rating device for the premenstruum. Other limitations include the absence of specific inclusion and exclusion criteria which limit the ability of the scale to translate changes in mood and behaviour into useful diagnostic categories, as well as inadequacies of Moos's normative sample since over half were taking oral contraceptives and nearly 10% were pregnant (Rubinow & Roy-Bryne, 1984). In view of Ruble's work on expectations (Ruble, 1977; Ruble & Brooks-Gunn, 1979), another limitation is the entirely negative wording of the scale, making it impossible to respond in a positive fashion.

Despite its limitations it remains the most widely used instrument. Apart from an unproductive attempt by Kashiwagi,

McClure, and Wetzel (1976), it was all that was available until the late seventies.

More recently, Steiner, Haskett, & Carroll (1980), responding to the success of Research Diagnostic Criteria (RDC) (Spitzer, Endicott, & Robins, 1978) for other psychiatric syndromes, combined the MDQ with the Multiple Affect Adjective Checklist (Zuckerman & Lubin, 1965), the State-Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970), several Visual Analogue Scales (Aitken (1969); Maxwell (1978)), the Hamilton Depression scale (Hamilton, 1960), and the Carroll Depression Scale (Feinberg et al., 1979), to produce RDC (table 1-2) and rating scales (appendix 2 and 3).

They identified eight major mood and behavioural symptoms, of which five are required for a positive diagnosis. While a tightening of diagnostic procedures is desirable, they have effectively reversed Moos's (1968) under emphasis of psychological symptoms (Rubinow & Roy-Bryne 1984). Somatic symptoms are only present in the rating scales. They also specifically excluded women with a psychiatric history in their sample and relegated such women to the status of having PMS secondary to such a disorder. The end result is certainly a more homogeneous group but at the cost of excluding many women with premenstrual complaints.

TABLE 1-2
RESEARCH DIAGNOSTIC CRITERIA FOR PREMENSTRUAL TENSION SYNDROME

PRIMARY RECURRENT PREMENSTRUAL TENSION DISORDER

This category is applied to female subjects in their fertile years who do not currently meet the criteria for any other psychiatric disorder.

The psychological and behavioural symptoms included in this disorder freguently occur in association with physical premenstrual symptoms, eg. painful or tender breasts, headaches, swelling of the abdomen, breasts or ankles, with water retention, weight gain, etc. These are not necessary for the psychiatric diagnosis.

A through D are required.

A) At least 5 of the following are required for definite and 4 for probable as part of a current episode.

1. irritable, hostile, angry, short-fused.
2. tense, restless, jittery, upset, high-strung, unable to relax.
3. decreased efficiency, fatigue.
4. dysphoria, marked spontaneous emotional lability, crying.
5. lowered motor coordination, clumsy, prone to accidents (cut finger, break dish etc.)
6. distractable, confused, forgetful, difficulty in concentration, lowered judgement.
7. change in eating habits (cravings, overeating etc.)
8. marked change in libido

B) overall disturbance is so severe that at least one of the following is present:

1. serious impairment socially, with family, at home, at school or work.
2. sought or was refered for help from someone or took medication (especially tranquillizers and/or diuretics) at least once during a premenstrual period.

C) premenstrual dysphoric symptoms for at least the six preceding menstrual cycles.

D) Symptoms only during the premenstrual period with relief soon after the onset of menses.

SECONDARY RECURRENT PREMENSTRUAL TENSION DISORDER

This category is applied for subjects who meet the criteria A through D for Primary recurrent premenstrual tension disorder but at the same time meet the criteria for another psychiatric disorder.

note. from "Premenstrual Tension Syndrome : The development of research diagnostic criteria and new rating scales" by M. Steiner, R. F. Haskett, and B. J. Carroll, 1980, Acta Psychiatrica Scandinavica, 62, p185.

The next attempt to structure the symptomatic picture was that of Abraham (1980). His major emphasis was the

identification of sub-groups based on clinical experience. Kerr's (1977) unsuccessful attempt to do this was criticised for being based on a presumed endocrinological substrate. Abraham (1980) delineated 5 symptomatic subgroups:-

(1) PMT-A. characterised chiefly by anxiety, irritability and nervous tension

(2) PMT-C. by premenstrual increase in appetite, cravings for sweets, headaches, palpitations, fainting spells and fatigue

(3) PMT-D. by depression, lethagy, confusion, withdrawal and suicidal ideation

(4) PMT-H. by hyperhydration with consequent weight gain and oedema

(5) PMT-P. by general aches and pains.

Abraham (1980) is critical of Kerr's (1977) presumption of aetiology, but does the same using nutrition in place of endocrinology. The 19 item scale is not soundly constructed, and includes questionable constructs (Rubinow & Roy-Bryne, 1984). Further, it has suffered poorly justified ad hoc modification. Begining as a reduced and re-ordered MDQ, PMT-P and 6 dysmenorrhea items have been deleted without rationale, and modifications to the MDQ food items (Abraham, 1980) are not justified until three years later (Abraham, 1983). Abraham has done little more than postulate another cause, and reduce the MDQ, with the likely consequence of decreased reliability.

The most recent development in this area is the Premenstrual Assessment Form (PAF), (Halbreich, Endicott & Schact, 1982; Halbreich, Endicott, Schact & Nee, 1982; Halbreich & Endicott, 1982). These authors have developed a

95 item assessment device together with two alternate scoring systems (unipolar and bipolar scales) and a classification schema. It is an attempt to provide descriptive clarity, measurement reliability and a valid classification system. It is the absence of these features which are responsible for the inconsistency in studies which attempt to relate biological changes to premenstrual changes (Halbreich, Endicott, Schact, & Nee, 1982). They are also critical of previous attempts such as Steiner et al., (1980) and Kashiwagi et al., (1976) because these provided a specific definition of a single premenstrual syndrome and thus avoided the issue of classification.

The arguments for classification are threefold (Halbreich & Endicott, 1982).

1). Differentiation aids investigative clarity with respect to patterns of change.

2). Differentiation helps clarify relationships between change and other variables.

3). Differentiation between affective and physical changes has already proved useful, (Kashiwagi et al., 1976; Wetzel, Reich, McClure, & Wald 1975; Diamond, Rubinstein, Dunner, & Fieve 1976; Cullberg, 1972).

Halbreich & Endicott (1982) favour a categorical rather than dimensional approach to classification (Maxwell 1972). Although this issue is peripheral to the current discussion, their conclusion that the advantage of the categorical approach is to facilitate the selection of subgroups of subjects, has a parallel with the disputed category of pseudodementia. In this sense they seem to be alluding to a treatment-diagnosis feedback process in which diagnosis is shaped by treatment response. This pragmatic, atheoretical

approach to management has advantages and is an intermediate step in developing theoretical understanding.

While accepting the need for subtyping, Halbreich & Endicott's (1982) evidence in support, is unconvincing. Kashiwagi et al., (1976), Wetzel et al., (1975), and Diamond et al., (1976) suggest affective symptoms may be PMS symptoms, but are more likely to be a substrate with premenstrual exacerbation. To this extent little has been added to Steiner et al.'s (1980) category of Secondary Recurrent Premenstrual Tension Disorder (table 1-2). Some support does come from Cullberg's (1972) findings that women without premenstrual irritability do as well on oestrogen dominant oral contraceptives as on placebo with respect to negative symptoms.

For any classification system, two questions need to be answered.(1) how adequate is the questionnaire on which the classification system is built. (2) how adequate is the classification system itself.

There is a need for a questionnaire which covers a broad but clear variety of symptoms, and is sensitive to change in severity (Halbreich, Endicott, Schact, & Nee, 1982) To achieve these aims the PAF differs from other procedures in four major ways, (1) individualised definition of the time period covered; (2) specificity of item definition; (3) broadness of coverage; and (4) focus on severity of change.

To some extent these differences have been achieved, but not without difficulty. The major problems are (a) the predominance of sophisticated retrospective judgements required of subjects; (b) the contradiction in practice of aiming for broad coverage and item specificity without undue length; and (c) the method of selecting items. The first, a

largely methodological problem, will be examined in greater depth in Chapter 4.

The second problem is illustrated by the question, "miss time at work because of premenstrual changes". To ensure coverage this requires other equally specific items relating to work performance. Instead they include the non-specific and vague question, "Have lowered performance, output, efficiency or ease in tasks at work, at home, or with hobbies etc".

Finally, an initial pool of 200 items, generated from the literature and suggestions of 40 female staff, was informally reduced, to 150, by deleting those items describing similar types of change. This was reduced to 95 items using item frequency and intercorrelations generated by 154 normal women recruited from research institute employees and student nurses. This assumes the only difference between PMS sufferers and normals is symptom severity. It is quite possible that a clinical sample would have resulted in different items being selected.

A classification system with subtypes would have considerable utility. Halbreich and Endicott's (1982) system emphasises the categorical or typological approach (Fliess, 1972), and has a dimensional parallel (Maxwell, 1972). The major strength of their typology is that it has no obvious aetiological basis. However, evidence in support of the typology is presented in the form of its ability to differentiate between sets of symptoms. This was the expectation that one set of symptoms will not occur in the presence of another set. Visual analysis of their table, they suggest, shows the degree of differentiation to be impressive. Certainly anxiety(nondepressed) and

irritability(nondepressed) discriminate quite well. However between 66-100% of subjects reaching the criteria for all categories (except anxiety(nondepressed)), are also classified as suffering from general discomfort. An additional problem is again the use of normal subjects. That they provide a more exacting test (Halbreich & Endicott, 1982) is debatable. Discriminant Function Analysis, on a clinical sample, would provide more impressive evidence.

This typology still has potential. The absence of an obvious aetiological model is a major strength. However, the critical test of any system is its ability to predict treatment response. The lack of speculation about what could function as therapeutic agents for each subtype, makes this more difficult.

Rubinow & Roy-Bryne (1984) suggest the PAF is the best way of selecting patients with similar symptom profiles. Its utility remains to be demonstrated with a clinical population. Despite this reservation, the PAF is the most promising, comprehensive, yet manageable device, currently available.

1-3 PREVALENCE

Given the diagnostic difficulties discussed above, it is not surprising to find major discrepancies in the estimates of prevalence (table 1-3). For example, Sutherland and Stewart (1965) found only three percent of their healthy sample were not classified as suffering from some premenstrual discomfort. They used a general definition, based on cyclicity with a loose timing requirement. By restricting symptoms to swelling, irritability, and depression they were able to reduce incidence to 38.7%. This left 58% of their young subjects claiming some discomfit

which was, in their view, of insufficient severity to be classified.

Prevalence estimates range from about 20% to almost 100% (Coppen & Kessel, 1963). It is difficult to partial out diagnostic variability, from variations in sample constitution. While under more ideal circumstances this latter variance would be of intrinsic interest, it adds to an already clouded picture.

TABLE 1-3

PREVALENCE OF PREMENSTRUAL SYNDROME

Authors	% with PMS	Study Sample
Bickers & Woods (1951)	36	Factory Workers
Rees (1953a)	44	Normal Women
Lamb, Ulett, Masters & Robinson (1953)	73	Student Nurses
Pennington (1957)	95	Normal Women
Appleby (1960)	29	GP Attenders
Coppen & Kessel (1963)	25	Community Survey
Sutherland & Stewart (1965)	39	Normal Women
Clare (1981)	77	GP Attenders

In essence, the prevalence of PMS, is unknown. Definitive statistics awaits the acceptance of more precise diagnostic procedures.

1-4 ASSOCIATED PHENOMENA

A considerable literature exists on the relationship between PMS and a variety of other conditions and behaviours, much of it confounded by methodological problems. The relationship between PMS and neurosis, and PMS and personality traits, is reviewed in chapter 3. The relationship between PMS and psychotic disorders,

dysmenorrhea, ovulation and contraceptive medication, suicide, and atypical episodic behaviour such as criminal acts, will be reviewed because of the relevance to methodological issues raised in this thesis. The large literature seeking evidence for menstrually related changes in objectively measured aspects of functioning, such as cognitive processing, and sensory sensitivity changes has been well reviewed by Parlee (1973) and is not central to this thesis.

1-4-1 Psychotic Disorder.

There are a number of studies that support the view that many reccurent psychotic illnesses become acute or florid more often in the premenstrual phase than would be expected by chance (Smith, 1975).

This literature has been developed, with particular respect to primary affective disorder (Kashiwagi et al.,1976; Diamond et al., 1976 and Haskett, Steiner, & Carroll, 1984). This has both theoretical and practical implications. The possibility that PMS may be a model for recurrent depressive conditions or that the reverse is possible, namely that endogenous depressive disorder may provide some understanding of PMS, is made explicit in Haskett et al., (1984). Their results provide no support for such a connection. The PMS group did not have the expected endogenous depression responses to the Dexamethasone Suppression Test and cortisol secretion.

The practical significance of the relationship between primary affective disorder and PMS is in the need to differentiate between PMS and premenstrual exacerbation of a preexisting condition. The importance of this discrimination is primarily methodological, particularly in the execution of

treatment trials. Whilst not denying the phenomenological significance of premenstrual exacerbation, it seems reasonable to exclude such women for trials designed to clarify etiology.

1-4-2 Dysmenorrhea

There is strong evidence for a clinical association between PMS and dysmenorrhea (Perr, 1958; Coppen, & Kessel, 1963; Argonz, & Abinzaro, 1950; Paulsen, 1961; Herzberg, & Coppen, 1970). However, they are differentially predicted by parity, increments in which are associated with increasing PMS and decreasing dysmenorrhea (Reid, & Yen, 1981). There is also evidence that PMS is associated with both ovulatory and anovulatory cycles, (Adamopoulus, Loraine, Lunn, Coppen, & Daly, 1972), whereas dysmenorrhea occurs with ovulatory cycles, (Reid, & Yen, 1981). It is clear from the attempts at defining PMS, reviewed above, and from the observations that the two disorders are frequently associated, that differentation is important in the selection of subjects.

1-4-3 Oral Contraceptives

Controversy exists with respect to the relationship between oral contraceptive use and PMS. Reid and Yen (1981) summarise the positive support for the use of these medications in treating PMS, as coming from uncontrolled studies (Moos, 1968; Mears, & Grant, 1962; Herzberg, Johnson, & Brown 1970; Royal College of General Practitioners, 1974; Kutner, & Brown, 1972; Nilson, & Solvell, 1962). These potentially confused PMS symptoms with those of dysmenorrehea (Perr 1958; Coppen & Kessel 1963; Argonz & Abinzoro 1950; Paulsen 1961; Herzberg & Coppen 1970). For most symptoms, large increases can be found amongst oral contraceptive users, while at most only a small decrease in PMS has been

noted (Royal College of General Practitioners, 1974; Mears & Grant 1962; Grant 1975).

Given the possible therapeutic status, and the interference to the basic hormonal substrate, subjects taking oral contraceptives should be excluded from trials. This does however potentially bias available subjects.

1-4-4 Infrequent Behavioural Events

Suicide and criminal acts such as violent offending have been frequently studied in relation to menstrual cycle phase.

MacKinnon, MacKinnon and Thompson's (1959) study on completed suicide, found 89% occurred within days 15-23 of a standardised menstrual cycle. They also found deaths by natural causes (84%), and accidents (90%) to have higher than expected frequencies. Birtchnell and Floyd (1974) and Buckle, Linnane, and McConachy, (1965) have criticised the assumption of a standard menstrual cycle and suggest the critical luteal phase ought to be defined in relation to the next onset of bleeding. This is especially important given the evidence that emotional stress can delay (Lloyd, 1962) or precipitate the onset of bleeding (Benson, 1964). If the luteal phase is determined by using the 12-16 days preceding the next expected menstrual period, then no significant differences were found in cycle phase for 76 attempted suicides (Birtchnell & Floyd, 1974). Birtchnell and Floyd (1975), matched 107 female suicide attempters with 110 age controls, and found comparable proportions of premenstrual emotional disturbance. Mandell and Mandell (1967) studying suicide prevention in 87 subjects suggested that there were peaks in first, middle, and last sevenths of a standardised cycle. In addition to the problems of actual cycle length, it is at least possible that women only perceive being early, middle,

or late in the cycle, and so respond in this fashion, (Clare, 1983)

The major studies that are frequently cited with respect to criminal acts are those of Morton, Additon, Addison, Hunt, and Sullivan (1953), and Cooke (1945). The former is methodologically sounder than most, but fails to state either the definition of cycle phase, or the method of determination (Parlee, 1973). Cooke's study merely cites the Parisian Prefect of Police who stated that 84% of all crimes of violence are perpetrated during the premenstrual or early menstrual phase.

Other infrequent behaviours that have been linked with the menstrual cycle include taking a child to a medical clinic (Dalton, 1966) and loss of control of an aircraft (Whitehead, 1934)

In essence the data linking infrequent but well defined behavioural events to the menstrual cycle are at best weak, and at worst unhelpful. Even if the association were clear cut, it does not logically follow, that women who have not emitted the behaviour are more likely to do so during a particular cycle phase (Parlee, 1973). Therefore, results reported in this literature, have no predictive power for the population at large.

CHAPTER TWO - BIOCHEMICAL THEORIES

2-1 INTRODUCTION

Given the methodological difficulties to be discussed in chapter 4, it is not surprising to find this area of literature in considerable disarray. It is also not surprising to find authors commenting on the lack of definitive progress in the fifty or so years since Frank (1931) first suggested the existence of a biochemical substrate for the syndrome (eg. Lancet Editorial, 1981).

The biochemical literature contains three major viewpoints. PMS is one homogeneous disorder, or a group of related syndromes, with menstrual cylicity in common, or alternatively, a disorder of centrally located biochemical processes, which act in concert with peripheral systems to produce a pathoplastic clinical picture (Reid & Yen, 1981)

Independent of which of these directions of investigation result in the most useful data, there are methodological difficulties that have a marked clouding effect. Subject selection procedures, the population studied, the use of retrospective self-report, and the varying symptom clusters accepted, are likely to lead to an initial over-reporting of symptoms, and, as a consequence, to the overvaluing of both drug and placebo responses.

A further complication in reviewing this literature is that most authors neglect to acknowledge interactions between the hormone systems or the relatively non-specific action of the various compounds used to alleviate symptoms and so provide evidence for the particular theory.

In this chapter of the review it is planned to (1) overview hormonal changes in the normal menstrual cycle, (2)

give a brief overview of each of the competing biochemical aetiological theories, and (3) evaluate the evidence supporting these.

2-2 HORMONAL CHANGES IN THE MENSTRUAL CYCLE

Steiner and Carroll (1977) summarise the menstrual biochemical process as follows.

> "In response to a hypothalamic releasing factor, the anterior pituitary produces follicle-stimulating hormone (FSH) which stimulates the development of the ovarian follicles and causes constant estrogen secretion during this phase of the cycle. Estrogen secretion rises to a peak at mid-cycle when, through a hypothalamic feedback mechanism, a surge of lutenizing hormone (LH) occurs together with a peak of FSH release. Ovulation then occurs and the corpus luteum begins to secrete progesterone. This is termed the luteal phase of the cycle. If fertilisation of the ovary has not occured, then progesterone secretion begins to decrease about 6 days prior to menstruation. Estrogen secretion from the ovary also begins to fall at about the same time" (p 323).

A variety of other hormone systems are reported as showing cyclical variation during the menstrual cycle. It is planned to review these briefly.

In a normal menstrual cycle there is a greater variablility of prolactin (PRL) secretion, during the luteal phase than exists within the follicular phase (Steiner & Carroll, 1977; Carroll & Steiner, 1978). It is clear from these reviews that variablility exists between women and potentially within individuals across cycles. The literature they cite fails to discriminate between normal and deviant cycles.

Adrenocorticotrophin hormone (ACTH) and cortisol show a cyclical pattern of lower follicular levels, modest increases at ovulation and a small decrease premenstrually (Genazzani, Lemarchand-Beraud, Aubert, & Felber, 1975). Limited methodological sophistication, in this study, makes these

observations difficult to accept at face value.

The mineralocorticoids, particularly aldosterone (ADS), has been studied quite intensively. A two fold increase in both ADS excretion in the urine and secretion rate has been reported (Reich, 1962; Gray, Strausfeld, Wantanabe, Sims, & Solomon, 1968; Schwatz & Abraham, 1975). ADS levels, in ovulatory cycles, reach a peak at about 9-10 days before menstruation and drop rapidly 6-7 days before bleeding begins (Katz & Romfh, 1972; Michelakis, Yoshida & Dormois, 1975). These changes were not found in annovulatory cycles. Other mineralocorticoids, such as desoxycorticosterone and corticosterone, follow a similar pattern (Schwartz & Abraham, 1975; Manlimos, Maroulis & Abraham, 1975).

A similar pattern also exists for plasma angiotensin, in that there are significantly elevated levels in the luteal phase when compared to the follicular phase, (Sundsfjord & Aakvaag, 1970). This is thought to be a function of increased progesterone secretion, during the luteal phase, which leads to sodium loss through the kidneys, which leads in turn to increased secretion of renin and angiotensin, which in turn leads to an increased secretion of ADS (Steiner & Carroll, 1977). The slightly lagged response in ADS to renin during the luteal phase supports this, (Katz & Romfh, 1972). as does the finding of no changes in plasma ADS levels or plasma renin activity in annovulatory cycles (Michelakis et. al., 1975), given that progesterone secretion does not rise during the luteal phase in such cycles.

Androgens, oestrogen and PRL are reported to show mid-cycle peak levels (Judd & Yen, 1973; Abraham, 1974; Abraham & Chakmankjian, 1973).

2-3 BIOCHEMICAL AETIOLOGICAL THOERIES

The first biochemical theory suggested reduced renal excretion of estrogen was responsible for PMS (Frank, 1931). This is possibly the only theory which considers oestrogen in the absence of progesterone and as such is considered crude. The field has increased considerably in sophistication since this time but as noted above this has not resulted in an equivalent progress. The review which follows is not exhaustive but rather illustrative of such endeavours.

2-3-1 Oestrogen/Progesterone Theories

Theories in this area are of 4 general forms, (1) a relative deficit of progesterone, (2) a relative deficit of oestrogen, (3) an idiosyncratic sensitivity to oestrogen, (4) withdrawal of either progesterone or oestrogen (Steiner & Carroll, 1977). These positions postulate either an oestrogen excess or progesterone deficit, the latter resulting in a relative oestrogen predominance, and are based on progesterone having a modifying effect upon oestrogen. Unopposed oestrogen results in fluid retention, breast enlargement and tenderness (Morton, 1950) and its accumulation in the limbic system causes the CNS manifestations of PMS (Backstrom & Mattsson, 1975).

Support for this position comes from using progesterone to significantly alleviate symptoms (Dalton 1964), oestrogen injections producing similar symptoms (Morton, 1950), and studies which link raised oestrogen levels, low progesterone levels, and high ratios of oestrogen/progesterone with symptoms (Backstrom & Mattsson, 1975; Munday, Brush, & Taylor, 1977; 1981). However there have been many reports of adequate corpus luteal function in patients with PMS (Bickers & Woods, 1951; Lamb, Ulett, Masters, & Robinson, 1953;

Andersch, Hahn, Wendestam, Ohman, & Abrahamsson, 1978; Gray, 1941; Greenblatt, 1940)

There is some evidence that premenstrual anxiety is associated with low progesterone or oestrogen alone (Backstrom & Carstensen, 1974; Backstrom & Mattsson, 1975). However insufficient detail makes interpretation difficult. It is possible that what makes the oestrogen/progesterone ratio significantly different between the experimental and control groups is a transient reduction in inter-subject variance. Subjects with premenstrual depression show no differences in plasma progesterone across phase and predictably show no improvement when treated with progesterone injections (Smith, 1975). Subjects who have responded to progesterone injections, suffered from anxiety, hostility, and irritability (Steiner & Carroll, 1977).

It is possible that these subgroups do reflect differential changes in the oestrogen/progesterone ratio, however double blind trials of progesterone have not shown significant results (Sampson, 1979). It is not clear what type of patient Sampson was using, and it possible that the doses used were less than Dalton's recommendations, which are greater than required to achieve normal luteal levels (Reid & Yen, 1983). It is possible that pharmacologic doses of progesterone may have some unknown central effects (Reid & Yen, 1983). This conclusion seems generous.

2-3-2 Vitamin Deficiency

The original interest in vitamin B complex was stimulated when a deficiency was found to impair oestrogen metabolism in rats. This was not confirmed in humans (Reid & Yen, 1981). Renewed support followed the discovery that vitamin B6 acts as a coenzyme (pyridoxal phosphate) in the

production of dopamine and serotonin (Dennerstein & Abraham, 1982) and significant improvements in a double blind trial of depression associated with oral contraceptives (Adams, Rose, Folkhard, Wynn, Seed, & Strong 1973). It is speculated that oestrogen generates, by altering tissue distribution and inducing competitive hepatic enzymes, a relative deficiency of B6 and therefore decreased serotonin, and dopamine, with depression and increased prolactin (Rose, 1969; 1978; Andersch, Hahn, Wendestam, et al. 1978; Halbriech, Assael, Ben-David, & Bornstein, 1976; Benedek-Jaszmann & Hearn-Sturtevant, 1976). If B6 could augment dopamine production then this should result in beneficial effects, however no study has demonstrated a significant dopaminergic effect (Reid & Yen, 1981). This casts doubt upon the rationale for using B6 in the treatment of PMS.

Uncontrolled trials, of B6, report positive results (Winston, 1969; Baumblatt & Winston, 1970; Kerr, 1977). However, a more controlled study was negative, (Stokes & Mendels, 1972).

2-3-3 Fluid Retention

An enormous amount of interest has been directed towards looking for factors causing fluid retention and evaluating diuretics as treatments (Reid & Yen, 1981).

Early work suggested PMS was the result of cyclic, ovarian activity induced, increases in extracellular fluids (Greenhill & Freed, 1941). If this occurred in the brain, gastrointestinal tract, or labia, then headaches, distention, or pruritis, respectively, will occur. This reflects a simplistic veiw of PMS symptomatology. What amounts to random changes have been found where weight change has been used as an indirect measure of fluid balance (Reid & Yen, 1981).

Studies using more sophisticated techniques found no differences between follicular and luteal phases in either total exchangable sodium or body water (Andersch, Hahn, Andersson, & Isaksson 1978; Preece, Richards, Owen, & Hughes, 1975).

While it has been suggested that there is a relationship between the degree of premenstrual weight gain and the severity of symptoms (Bickers & Woods, 1951; Abramson & Torghele, 1961; Janowsky, Berens, & Davis, 1973), most authors have not been able to establish a pattern of weight gain, (Mattsson & Schoultz, 1974; Bruce, & Russel, 1962; nor find any relationship between degree of fluid retention and severity of PMS symptoms other than oedema (Appleby, 1960; Bruce & Russell, 1962; Golub, Menduke & Conley, 1965; Lamb, Ulett, Masters, & Robinson 1953).

Controlled studies of diuretics failed to find significant improvement (Mattsson & Schoultz, 1974; Jordheim, 1972; Andersch, Hahn, Andersson & Isaksson, 1978).

The lack of support for fluid retention, has not deterred investigators and some of the more elaborate hormonal/neurotransmitter propositions involve this fluid retention concept.

2-3-4 Renin-Angiotensin-Aldosterone (RAA) Axis

A close parallel between negative affect scores and body weight, lead Janowsky et al. (1973), to speculate that the underlying mechanism could be the direct action of angiotensin. However, they confuse depression and irritability, and more recent studies suggest that RAA activity decreases at around 6 days preceeding menstruation, thus making its involvement unlikely. In addition, there is evidence for PMS in annovulatory cycles (Adamopoulous et al.,

1972), where RAA and progesterone levels are not variable (Steiner & Carroll, 1977).

The position is, indeed, more complex in that (1) both oestrogen and progesterone interact with the RAA axis, (2) both oestrogen and progesterone act independently with respect to fluid retention, (3) there is a relationship between dopamine and ADS excretion, and (4) stress or anxiety is known to enhance ADS excretion (Reid & Yen, 1981).

At this stage, given the additional contentious nature of the fluid retention literature, the involvement of the RAA axis, remains inconclusive.

2-3-5 Prolactin

Self-observation, by Horrobin, following injection of PRL, first suggested the idea that it could play a major role in the premenstrual syndrome (Reid & Yen, 1981; Carroll & Steiner, 1978). More specifically, premenstrual depression may be the result of elevated PRL levels in conjunction with high oestrogen or progesterone dominance, and premenstrual irritability, elevated PRL levels with low progesterone (Carroll & Steiner, 1978).

The major evidence cited in support of this position is the study by Benedek-Jaszmann & Hearn-Sturtevant (1976). However, these authors did not impressively demonstrate high PRL nor cyclic changes, nor did they adequately specify what psychological disturbances were suffered by their subjects. Further confusion results from the use of subjects recruited for an infertility clinic with annovulatory cycles and short luteal phases.

Halbriech, et al. (1976), are also cited as providing direct evidence for the PRL position (Steiner & Carroll, 1978). However, these authors suggest that previous studies

show no cyclical changes in PRL secretion and their findings were characterised by large individual variation. They also found no correlation between serum PRL and symptom rating scales, and stress related increases in serum PRL.

The PRL hypothesis is also linked to the contentious fluid retention literature, on the basis of an association between premenstrually occuring oedema and dysphoria, and that it is the only hormone which leads to retention of water, sodium, and potassium (Steiner & Carroll, 1978).

Reid and Yen (1981) extend Steiner and Carroll's review and come to the opposite conclusion. Some recent studies have found elevated luteal phase PRL levels in PMS patients (Andersch, Hahn, Wendestam, et al., 1978), while other findings have been equivocal (Andersch, Abrahamsson, Wendestam, Ohman, & Hahn, 1979; Anderson, Larsen, Steentrup, Svendstrup & Nielsen, 1977). Controlled clinical trials of bromocriptine, a PRL suppressant, in the treatment of PMS has produced largely equivocal or negative results (Andersch, Hahn, Wendestam, et al., 1978; Andersch, Hahn, Anderson et al., 1978; Anderson, et al., 1977; Graham, Harding, Wise & Berriman, 1978; Andersch, et al., 1979; Ghose & Coppen, 1977).

A more recent review of controlled studies using bromocriptine, includes aditional studies (Andersch & Hahn, 1982; Barwin, 1980; Elsner, Buster, Schindler, Nessim & Abraham, 1980; Kullander & Svanberg, 1979; Ylostalo, Kauppila, Puolakka, Ronnberg & Janne, 1982), but concludes that there is little support for bromocriptine as a treatment for PMS, beyond symptomatic relief (Andersch, 1983).

In summary the elaborate theorising with respect to PRL has not resulted in much empirical support nor effective

treatment. That does not necessarily mean that PRL has no role in generating PMS symptoms but that methodological inadequacies are likely to have obscured its involvement.

2-3-6 Endogenous Hormone Allergy

A positive skin reaction to injection of steroids in women with severe PMS (in the absence of such an effect in normal controls) has lead to hypersensitivity to endogenous hormones or their metabolites being suggested as a possible cause of PMS (Zondek & Bromberg, 1945; 1947). Uncontrolled studies report an overall 80% success rate, (Henkle, 1951; 1953; Rogers, 1962; Simmonds, 1956). As skin reactivity is extremely sensitive to several extraneous variables (Henkle 1949; 1951; Henkle & Scherp, 1955) such evidence is seen as insufficient (Reid & Yen, 1981).

2-3-7 Neuropeptides

A central and pituitary based cause of PMS, involving the neuropeptides beta-endorphin and alpha-melanocyte stimulating hormone, has been suggested (Reid & Yen, 1981) They cite some lower animal research to support this position. The central effects, in sensitive subjects, of these neuropeptides, and their ability to modify the action of neurotransmitters, may produce changes in mood and behaviour, as well as affecting the release of other pituitary hormones such as prolactin and vasopressin. Individual variation in peripheral hormone response to these events, could account for the heterogenous clinical manifestations observed in PMS (Peck, 1982)

Beta-endorphin has a complex and interactive function, with raised levels being associated with, decreased luteinizing hormone, decreased prostaglandin E1, increased PRL which further decreases progesterone and leads to an

increase in oestrogen/progesterone ratio, decreased dopamine which leads to an increase in ADS activity and consequent fluid retention, as does the increase in vasopressin activity with its associated rise in ACTH and ADS (Peck, 1982). An increase in b-endorphin is also associated with insulin release and consequent changes in blood sugar and appetite.

This is plausibly complex. Naloxone, a beta-endorphin antagonist was given to 12 women in a double-blind trial over 2 cycles (Peck, 1982). Both placebo and naloxone significantly reduced stress scores when compared to the baseline level of stress. However the placebo resulted in significantly greater improvement than naloxone. Peck speculates that naloxone could have had an aggravating effect and that this could be a result of excessive rebound to dopaminergic hyperfunction. She neither re-examines the data for a predominance of specific dopaminergic symptoms nor does she present enough detail for this to be deduced.

It is not clear from either Peck's (1982) study or that of Reid & Yen (1981) what the relationship is between beta-endorphin and alpha-melanocyte stimulating hormone. It seems possible that if naloxone is a specific antagonist to b-endorphin then Peck's study is not an adequate test of the hypothesis. It is also possible that subject selection factors are again obscuring actual relationships.

2-4 SUMMARY

None of the above aetiological hypotheses, nor the pharmacological treatments derived from them, have survived double blind trials. The lack of methodological rigour and compatibility make it difficult to compare studies. In short little progress has been made since Frank's (1931)

identification of the syndrome (Lancet Editorial, 1981).

CHAPTER 3 - PSYCHOLOGICAL THEORIES AND TREATMENTS

3-1 INTRODUCTION

Literature on psychological approaches to PMS is relatively sparse. What is available falls into two major groups: (1) Historical studies, that relate and implicitly explain the PMS on the basis of personality variables. (2) Those more recent studies which examine social attitudes and associated attributional processes. These two approaches, while being dealt with separately in this review, are strongly related since the second is a more sophisticated outgrowth of the first. A third, minor aspect of the current literature concerns evolutionary/sociobiological writing on the premenstrual syndrome.

The role of psychological factors is often disputed. For example, some authors suggest that both psychological and psychosocial factors account for a minor proportion of the variance (Rees, 1953a; James & Pollitt, 1974; Steiner & Carroll, 1977). Others suggest there is considerable evidence supporting the importance of psychological and enviromental factors (Dalton, 1964; Coppen & Kessel, 1963; Janowsky, Gorney, & Kelley, 1966; Janowsky, Fann, & Davis, 1971; Janowsky et al., 1973).

The point argued in this section of the review is that neither of these positions are adequate. This area, together with the biologically oriented literature, frequently fails to appreciate that correlation does not imply cause. In the rare occasions that this is acknowledged, predictably the evidence is for a moderate position of multiple cause. The other major confusion in this area is that frequently authors have focused upon total menstrual cycle related distress rather than the distress related specifically to the

premenstrual phase.

3-2 PERSONALITY THEORIES

Some of the earliest work in this area was from writers of an analytic orientation. As such, the manifestations of PMS were seen as reflecting intense unconscious conflicts concerning the female role (Deutsch, 1944; Benedek, 1952; Benedek & Rubenstein, 1939a; 1939b; Israel, 1938). More specifically, PMS is related to a lack of acceptance of menstrual function. Menstruation is used to express distress which results from other conflicts about enviromental situations, interpersonal difficulties, pregnancy and related issues. As such menstruation symbolises either a lost child or femininity.

There are many problems with the psychoanalytic model. One major problem for the theory is the central position given to menstruation, in that the bulk of the psychological symptoms occur before menstruation (Rausch, Janowsky, Risch, Judd, & Huey, 1982). This may be one of the reasons for the menstrual/premenstrual confusion mentioned above. The other major problem, in common with other theoretical models is that of correlation vs causality. Pathology and aetiology have also been confused in this early work (Veit, 1955), in that dynamic explanations are often just additional descriptions of current pathology. Examples of this are, dysfunctional mother/daughter relationships (Deutsch, 1944), dysfunctional father/daughter and husband/wife relationships (Israel, 1938), and disturbance in pre-pubertal development, (Veit, 1955).

Recent literature is less speculative. For example, high premenstrual tension scores are related to more disturbed family relationships, viewing the menarche and menses as

stressors and sources of unhappiness, and feelings of being less adequate with respect to psychosocial and psychosexual roles (Paulson, 1961).

Levitt and Lubin (1967), Paige (1971), May (1976), Fortin, Wittkower, and Kalz (1958) and Shainess (1961) are similar in that they each relate menstrual symptoms to outdated personality models and conclude descriptively about negative menstrual attitudes and their origins.

Suarez-Murias (1953) and Lamb et al. (1953) differ from this trend. They indentify problems with such factors as marital status, emotionality, life stressors, maternal symptoms, preparation and attitude to menarche and menstruation, and abnormalities in psychosexual development. The real factors are personality type and the enviromental setting (Suarez-Murias, 1953). The latter point has been developed more fully within an attribution framework, the former in the literature looking at the neurotic personality.

More recent literature has attempted to relate menstrual and premenstrual complaints to neuroticism and a generalized psychosomatic complaining (Smith, 1975). PMS has been found to have a higher prevalence in psychiatric patients than in normals (Rees, 1953a). While there were no between-group differences on emotional instability or neurosis there was a positive correlation between neurotic constitution and PMS. What is meant by these labels is unclear. Poor work record was the only discriminably different item of all those listed for both emotional instability/neurosis and neurotic constitution. The positive correlation between severity of neurosis and severity of PMS, and between severe PMS and maladjustment, are similarly difficult to evaluate.

In a futher study of 30 women with severe PMS, Rees

(1953b) concluded that PMS is not primarily a form of neurosis, on the grounds that it almost always predates the neurosis and further, improvement in either condition is independent of the status of the other.

A study of 500 normal women found symptoms such as irritability depression and tension were at a maximum premenstrually, and these symptoms together with headaches and swelling around the menstrual period were significantly associated with Maudsley Personality Inventory (MPI) neuroticism scores (Coppen & Kessel, 1963). These findings are difficult to evaluate. Of the correlations reported, the shared variance accounted for is low, ranging from 3.8% to 6.6%. Another problem is that the correlations appear to be calculated without reference to where in the cycle symptoms occured. Thus it is not possible to clarify the combined relationship. An extension of this work to psychiatric patients (Coppen, 1965) found neurotics but not those with affective disorders or schizophrenia had, compared with controls, an increased frequency of irritability and depression premenstrually with menstrual pain and headaches. Coppen's conclusion of a strong association between PMS symptoms and MPI neuroticism is selective given most menstrual problems in psychiatric patients show this relationship. It is possible that menstrually related symptoms are epiphenomenal to the psychiatric disorder. This work has also been criticised because the MPI neuroticism scale contains questions a sufferer would answer positively as a result of having PMS, rather than these responses being a reflection of neuroticism (Smith, 1975). Coppen maintains the association remains after the removal of the offending items.

A later study (Kramp, 1968) does little to clarify the position. Of 131 women referred for psychiatric evaluation prior to an abortion, 52% of the 50% that suffered PMS are reported as having had a neurotic disposition in childhood or early youth.

In summary, there is likely to be a group of women that are anxious and may have sex-role adjustment difficulties, and are statistically more likely to complain of premenstrual irritability (Smith, 1975). There are also many non-neurotic persons who suffer similarly. There are strong parallels with pain and alcohol research in that considerable effort has been expended in the identification of personality characteristics of both of these patient groups, and with similar lack of success. This is not suprising given the outdated personality models these researchers use.

3-3 ATTRIBUTION THEORIES

Parlee's (1973) review of the menstrual literature has had two direct consequences. Firstly the literature examining the personality characteristics of women with premenstrual distress has decreased in rate. Secondly there has been an increasing amount of theoretical and empirical work being done within a social psychological framework using attribution theory. It is proposed to examine these theoretical and empirical aspects separately.

3-3-1 Theoretical Position

The menstrually related literature is based upon an assumptive model that sees physiological processes as causes with psychosocial phenomena as effects (Ruble, 1977; Parlee, 1977; Sherif, 1980). As such it is both a physiologically reductionist and deterministic model. The literature is fraught with methodological problems and rare achievements of

experimental requirements. Hence a causative model is premature if not inaccurate. Menstrual processes could conceivably be a reason for distress not the cause. Performance deficits, beyond olfactory and tactile sensitivity, are poorly supported and there is little strong empirical evidence for the majority of women suffering severe cyclic changes on any parameter (Ruble & Brooks-Gunn, 1979).

An alternative explanation is that the belief in a cyclic, hormonal, debilitating phenomenon is held by researchers and their subjects (Ruble & Brooks-Gunn, 1979; Parlee, 1974), and may in turn influence the existence of these symptoms. This risks medicalisation of a normal state (Lancet Editorial, 1983).

Extreme positions are taken. The finding that women rate themselves and women in general similarly with respect to symptoms, has been used to suggest they are therefore reacting to or reflecting cultural stereotypes (Parlee, 1974). It is possible that such reports indicate only that symptoms associated with the menstrual cycle are common knowledge across groups, rather than that the self-report reflects other than their own experience (Ruble & Brooks-Gunn, 1979). Another argument for the operation of cultural stereotypes is that males, over a 35 day period, show similar variation in mood and concentration difficulties, to women (Sherif, 1980). Given Sherif's sample did not suffer from PMS, the lack of difference is not surprising.

Aside from these extreme positions, the important question is, how can the development and persistence of such biased or erroneous beliefs be explained. Ruble & Brooks-Gunn (1979) suggest attribution theory can do this and present a

cogent exposition of the possible mechanism. The diagnosis of premenstrual change involves the use of two subjective and ambiguous sets of information by either the subject or, with more difficulty (Irwin, Kammann, & Dixon, 1979), by an observer. These are symptoms and the phase of the cycle. Using these sets of information, the judge must decide if she feels or behaves differently during the premenstrual or menstrual phase of the cycle. This involves a considerable range of possible behaviours and a large span of time. It is likely that differential attention will occur and bias perceptions (Ruble & Brooks-Gunn, 1979). Evidence from the cognitive and social psychological literature supports the bias involvement in such tasks (Tversky & Kahneman, 1974).

Ruble & Brooks-Gunn (1979) suggest negative beliefs about menstrual events may be acquired via three mechanisms. Firstly, if events share subjectively similar characteristics they can generate plausible, but fallacious causal connections (Nisbett & Wilson, 1977; Tversky & Kahneman, 1974). Secondly, distinctive events lead to focusing of attention, and so two temporally contiguous distinctive events frequently lead to illusory correlations (Chapman & Chapman, 1967; 1969). Thirdly, the joint occurrence of any two events is remembered best. Menstrual phenomena tend to be distinctive, and perceived negatively by a proportion of the population, as are negative moods and uncomfortable physical symptoms. It is therefore possible that some of the reported discomfort results from the negative expectations acquired in these ways.

The strengthening of such negative beliefs and expectations, can happen in three ways (Ruble & Brooks-Gunn, 1979). Firstly, distortion of evidence occurs to generate

maximum consistency, particularly if the data are ambiguous. Secondly, evidence for a belief tends to be detached from the belief itself, and thirdly the accessibility of evidence is at least in part a function of how the information is labeled and coded.

In summary, Ruble & Brooks-Gunn (1979) are suggesting that at least some of the negative symptomatology surrounding the menstrual cycle is the result of socio/cultural beliefs generated by the above mechanisms. This is opposed to the view that all such symptomatology is determined by the biological substrate. They do not deny these latter factors are important in generating individual differences, but suggest that they are insufficient on their own.

3-3-2 Empirical support

The proposed mechanisms of acquisition are supported in a study which found menstrually related phenomena were used to explain negative but not positive moods, even when the environment was described as unpleasant (Koeske & Koeske, 1973). These findings are consistent with the first two acquisition propositions but, being cross-sectional, are unable to support the third. Their findings also support the proposition that evidence is distorted, as does the finding that similar behaviours are evaluated differently when they are associated with menstrual or premenstrual days compared with other times in the cycle (Ruble, 1977).

It is possible that natural variation in cycle length leads to less awareness of the premenstruum. Oral contraceptive users, with regular cycles, made more menstrual cycle attributions for symptoms occuring premenstrually than non-users (Campos & Thurow, 1978). However, this is weakened by possible pharmacological effects and the failure to

acertain if non users were in fact less able to predict the onset of menstruation.

The lack of cyclicity in hysterectomised subjects (Beumont, Richards, & Gelder, 1975) is support for the attribution position (Osborn, 1981). However, continuing symptoms have been found (Backstrom, Boyle, & Baird, 1981).

Strong support comes from studies which have attempted to conceal the purpose of the study and found few cyclic changes (Englander-Golden, Whitmore, & Dienstbier, 1978) or compared retrospective report and prospective tracking (Endicott & Halbreich, 1982) and found less evidence for cyclical changes in the latter instance. Futher indirect support comes from the high placebo rates reported in double-blind drug treatment trials.

In summary, the existence of a set of consistent and negative beliefs surrounding menstrually related phenomena is reasonably well supported, and no doubt contributes to biased reporting. The interesting questions remain. What proportion of the variance can be accounted for in this fashion? What intervention is likely to succeed?

CHAPTER FOUR - METHODOLOGICAL PROBLEMS

4-1 INTRODUCTION

The major emphasis of the research reported in chapters five, six, and seven is to evaluate methodological changes designed to overcome problems that exist in this area. Some of these problems will be considered systematically in this section, as well as being mentioned elsewhere.

Subject selection is reviewed in section 4-2. Some of the central methodological issues to the conventional diagnostic process were reviewed in chapter one, for example, heterogeneity of symptoms and negatively phrased questions. However the critical diagnostic aspect of PMS, the time dimension, creates specific problems for measurement strategy, and in the detection of cyclicity. These are reviewed in sections 4-3 and 4-4, respectively.

4-2 SELECTION OF SUBJECTS

Ideally, there is increasing use of more diverse populations of subjects as any area of research develops. This helps determine the generalisability of the conclusions reached. In the PMS literature this process has been distorted in two ways.

Firstly, subjects' origin and characteristics are often so poorly described, that it is not possible to adequately interpret the results nor integrate them into a wider framework. For example, Barr (1984) gave no description of his 48 subjects, and also failed to report data of 12 subjects in the active drug condition, and 18 in the placebo condition. Muse, Cetel, Futterman, and Yen (1984) reported race, education, parity, but not age, of the 50 women who sought evaluation and treatment. However, only 8 were used,

the remainder were dropped for reasons as diverse as having a psychotic profile or not being judged sufficiently dependable and motivated. No other details were provided. Dalton (1984), similarly reported no details of subjects other than the fact that 31 volunteered to help in the study.

Secondly, many of the populations studied are too extreme to be credible especially when the range of aetiological possibilites are considered. Rubinow and Roy-Bryne (1984) list some of the sources of subjects in studies which purport to address the question of menstrually related mood disorders ie., PMS clinics (Sampson, 1979), infertility clinics (Benedek-Jaszman & Hearn-Sturtevant, 1976), women undergoing gynecological surgery (Beumont et al., 1975), general practitioner patients with and without symptoms (Robinson, Huntington, & Wallace, 1977; Clare, 1977), college students (Moos, 1968), normal women with no changes (Taylor, 1979; May, 1976) and normal women with symptoms but not requesting treatment (O'Brien, Craven, Selby, & Symonds, 1979).

PMS clinics are a reasonable source. Similarly a case can be made for using subjects showing symptoms while not receiving medical treatment, given the controversial nature of the disorder. However the use of an infertility clinic sample is indefensibile, given the likely presence of unusual stressors and possible hormonal substrate differences. Although admirable because of its attempt to avoid menstruation as a marker for cycle position (Osborn, 1981), Beumont et al's., (1975) study on women undergoing hysterectomy, illustrates an unusually narrowly selected and potentially highly stressed group of subjects.

The method of selecting subjects from within a

population is rarely discussed. One aspect of this selection is the criteria for inclusion. Criteria such as menstrual regularity, mechanical methods of contraception, absence of psychiatric or physical disorder and absence of drug taking have been used (Steiner et al., 1980; Steiner, Haskett, Carroll, Hayes, & Rubin, 1984; Steiner et al., 1983). These are a minimum, but rarely specified requirement.

The second aspect to selecting within a population is how adequately do retrospective questionniares predict future symptom occurrence. This issue is reviewed in section 4-3.

4-3 MEASUREMENT STRATEGIES

One of the eariest reports expressing doubt about the adequacy of retrospective report is that of McCance, Luff, and Widdowson (1937). Disrepancies between data collected daily from 167 women, over 4-6 cycles, and preliminary questions, were " so frequent that they throw considerable doubt upon the value of any work on this subject based upon history or a questionnaire"(p576). This warning has gone almost entirely unheeded until recently. Other evidence to support this contention comes from Abplanalp, Donnelley, and Rose (1979) who found the pattern of significant interphase differences reported on thrice monthly MDQ administrations, were not replicated in daily Profile Of Mood States records, at least with respect to negative affect. In a sample of college women (mean age 22 years), May (1976) found no relationship between subjects' mood changes assessed at three points during the menstrual cycle and their retrospective interview accounts. Golub (1976) similarly found no correlation between complaints of premenstrual symptoms and mood score obtained during the premenstrual phase. While presenting no data, Sampson and Prescott (1981) referred to

an unpublished paper by Sampson (1980) in which only 60% of cycles showed agreement between daily self-rating and retrospective rating. Brockway (1975) (cited in Abplanalp, Donnelley, & Rose, 1979) measured subjects' daily rating during two cycles for pain, water retention, and negative affect, and compared these with the retrospective form of the MDQ. No relationship was found for pain or negative affect. The two month prospective use of Visual Analogue Scales for depression and anxiety confirmed self-diagnosis in only 8 of 20 subjects (Rubinow, Roy-Bryne, Hoban, Gold, & Post, 1984)

Endicott and Halbreich (1982) set out to directly test the degree of confirmation possible using daily ratings compared to the PAF. They were able to do this for 59% of their sample of 48 women. Within severity categories, they found confirmation rates varied from 42%, for subjects rated mild, to 87% for those categorised severe. Only 57% of subjects who rated themselves as having no symptoms had these ratings confirmed. Three subjects were found to have mild levels of premenstrual change despite claiming no symptoms retrospectively. For those subjects claiming symptoms, the major reason for disconfirmation was high non-premenstrual scores. An additional mid cycle interview would not have helped as most of the 41% reported feeling well for a few days around mid-cycle followed by deterioration, with minimal premenstrual exacerbation.

The only study to report successful prediction of PMS used the Steiner et al (1980) scales and related them to selected portions of one and a half cycles of daily ratings on the Profile of Mood States and an unspecified somatic symptom scale (Haskett, & Abplanalp, 1983). This study was highly selective, using only 24 out of 130 applicants and

found that up to two or three cycles were needed to successfully schedule interviews in the follicular and late luteal phase.

With the exception of Abplanalp et al., (1979) and Rubinow, Roy-Bryne, Hoban et al., (1984), the major difficulty with most of these studies is that no data are presented to illustrate the conclusions drawn, nor are details provided of the prospective device used. It thus remains possible that the results are a function of a lack of overlap between the domains sampled with the different methods of collection, rather than the methods of collection themselves. Other difficulties are the preoccupation with mood data instead of the range of possible symptomatology, and the lack of a direct test regarding the predictive power of the retrospective interview when compared to prospectively collected data.

Confirmation of interview data by prospectively collected data is one aspect of this problem. Prospective studies frequently address the reliability of a retrospective instrument, when daily records have been kept between the first and second administration. Decreased scores have been found on the second retrospective test compared to first administration (Harrison, Endicott, Rabkin, & Nee, 1984; Endicott & Halbreich, 1982). The interpretation of such results highlights two problems.

1. Dimensional v's categorical scales. Harrison et al. (1984) rated their 12.6% reduction in score as trivial. Using PAF diagnostic categories, Endicott and Halbreich (1982), however, found a decrease from 41 to 27 in the number of subjects reaching the criteria for major depressive syndrome.

2. Expectation of constancy. Harrison et al, (1984)

suggest the decrease could have been the result of subjects correcting their retrospective falsification of symptom severity or the psychological support provided in the interim. Falsification is a perjorative term when compared with alternative explanations. It is possible that subjects are simply unable to respond accurately. The timing of interviews with respect to the menstrual cycle is not specified, but appears fixed and so independent of cycle length. Thus subjects are likely to be rating themselves at different points in the cycle. This is likely to induce change (Ruble 1977). Another possible explanation is that the severity of symptoms does fluctuate from month to month. This raises the issue, as does Endicott and Halbreich's (1982) paper of whether it is realistic to expect consistent levels of severity across cycles. One cycle of prospective data collection is inadequate to clarify these points.

Overall there is reason to be suspicious of data collected entirely from retrospectively oriented questionnaires, particularly with respect to mood or emotional dimensions. The questions of how this applies to physical symptoms, how well such data predict subsequent daily scores, and the impact of viewing a larger number of cycles on the conlusions drawn, remain to be answered. It is also noted that prospective devices are unlikely to be entirely free from distortion (Ruble 1977), they reduce some inaccuracy, but are still influenced by stereotypic beliefs.

4-4 CYCLICITY

While symptom heterogeneity has been the subject of much discussion, the issue of cyclicity has been poorly discussed until very recently. The historical tradition has been simply to report a temporal association between the symptomatology

and the menstrual cycle. This is inadequate on several grounds intrinsic to the concept of cyclicity. For the sake of clarity, at least three related but divisible aspects of cyclicity must be considered: (a) what period of time, with respect to the menstrual cycle, is defined as the premenstruum, and as such is the critical period for symptom occurrence; (b) what is the baseline against which these symptoms must be evaluated; (c) how many symptomatic cycles are needed to eliminate the hypothesis of chance fluctuations.

4-4-1 Definition of Time Period

While it is accepted that considerable inter-subject variability does not invalidate the label PMS, the variability in defining the premenstruum is unhelpful. For example Kramp (1968) defines "premenstrual" as the last six days of the luteal phase and the first two days of menstruation while Taylor (1979) suggests that most symptoms are "perimenstrual". These are illustrative of definitions that cause confusion, particularly with respect to dysmenorrhea. Halbreich, Endicott, & Schact's (1982) definition in the PAF takes a more idiographic position by suggesting in their instructions to subjects that the premenstrual period may range from one to fourteen days. They further suggest each woman should determine the duration of her premenstrual period using physical, behavioural and mood changes as guides. These are considered to be part of the premenstrual period if: (a) they appear or change during the premenstrual period ; (b) they do not exist in the same form or severity immediately prior to the premenstrual period ; (c) they disappear or return to usual state during the full flow of menses. In other words they pass the responsibility

for defining the premenstruum to the subject and appear to allow the inclusion of symptoms after the onset of menstruation. While it is perhaps unreasonable to expect instantaneous relief from symptoms coincident with the onset of bleeding (as is implicit in some of Sutherland & Stewart's, 1968, objections to the term premenstrual tension) it has been suggested (Soule, 1960; Reid & Yen, 1981) that similar symptoms can and do occur during menstruation and post-menstrually, particularly at mid cycle (Geiringer, 1951).

Norris (1983) expands the temporal definition to include most of the above concerns; "we define the premenstrual syndrome (PMS) as a wide variety of adverse signs and symptoms that occur regularly in the same phase of each menstrual cycle, followed by a symptom-free phase in each cycle"(p509). The breadth and inclusiveness of this position creates problems, as does Steiner et al's., (1980) suggestion that symptoms can only occur during an unspecified premenstrual period with relief soon after menses.

The little consensus that exists suggests, in the absence of a unifying cause, symptoms ocurring outside of an approximate ten day period immediately prior to menses should be excluded, if only for the sake of investigative clarity. While allowing 24-36 hours after the onset of menstruation for the subsidence of symptoms, it also is important to exclude those symptoms likely to be a direct result of bleeding such as dysmenorrhea.

4-4-2 Baseline Measurement

Most of the symptoms of PMS can and do occur for a variety of reasons at a variety of times independent of the menstrual cycle (Lancet Editorial, 1981). Coppen and Kessel

(1963), Geiringer (1951), and Sampson and Jenner (1977), have shown women to be symptomatic at other times. This problem was responsible for the bulk of the disconfirmations in the Endicott and Halbreich's (1982) study. The interpretation of such data is almost inevitably in terms of premenstrual exacerbation of some underlying condition. While this is possible, the inverse has been rarely considered. Wilcoxon, Schrader and Sherif (1976) have suggested that stress is more related to symptoms than the menstrual cycle phase. While this is indirectly contradicted by the lack of consistent menstrual cycle phase related differences in plasma cortisol between sufferers and nonsufferers (Steiner, Haskett, Carroll, Hays, & Rubin, 1984), the possibility that the symptoms and the premenstrual phase of the menstrual cycle may be epiphenomenal is important. The number of cycles in which there is a significant degree of change in the premenstrual period, ie., consistent expression is seldom discussed. Steiner et al., (1980) state six cycles are needed, but not why. More frequently it is not discussed at all. In part this reflects an implicit assumption about the nature of the disorder, ie., a constant defect in the endocrinological, metabolic or psychological substrate which causes symptoms in the appropriate portion of the menstrual cycle. Other assumptions could be made about the aetiological substrate which would lead to different expectations about consistency over cycles. However, selecting only consistent subjects is reasonable. The advantages are the ability to evaluate treatments over a practical length of time, and some degree of homogeneity within the population being studied. This does not, however, overcome the problem of chance association between symptoms and the premenstrual phase. This

is a major problem for studies which examine one cycle and only measure symptoms once during the premenstruum.

Other points raised by the concept of baseline are that of the measurement of change rather than absolute severity (Rubinow and Roy-Bryne, 1984; Halbreich, Endicott & Schacht, 1982), how much variation is acceptable for exclusion as "normal" (Parlee 1973), and which other part of the cycle one uses as the contrast (see sec 4-4-1, for the range of possibilities which exist).

4-4-3 Determination of Cyclicity

Firstly, there is explicit reference in almost all definitions of premenstrual syndrome, to cyclicity and cycle phase, but few attempts exist that qualify this in any rigorous fashion. Secondly, there have rarely been ackowledgements (eg. Lancet Editorial, 1981; Sampson & Jenner 1977) that the symptoms can occur in response to stressors and so exist premenstrually by chance. These two methodological issues are to a degree inseparable, in that to establish the former, avoidance of the latter is a prerequisite. It is not sufficient merely to state the existence of cyclicity as a considerable number of authors have done (eg., Backstrom & Mattsson, 1975; Clare 1977; Osmun et al. 1983). Nor is it sufficient to state the number of cycles in which symptoms have to occur (Steiner et al. 1980).

Authors who have attempted to quantify cyclicity are limited to those few studies of longitudinal design and true prospective daily recording. Such authors have used three techniques to achieve this.

1. Difference scores.

O'Brien et al., (1979) exemplify the use of difference scores, in an attempt to quantify cyclicity. The difference

between follicular and premenstrual score was used as a single indicator; a positive score indicating a symptomatic cycle. While this satisfies the requirment of detecting change rather than absolute level (Rubinow & Roy-Bryne, 1984) it raises the issue of establishing a baseline. A decrease from a euphoric mid-cycle state, to average mood during the premenstruum would, by this system be scored as a symptomatic cycle. Another issue is how to define a significant increase in difference. Steiner (personal communication, August 3, 1983), in reference to twice monthly use of the premenstrual rating scale, suggests any difference is significant. This ignores the likely possibility of some random fluctuations and trivial variance (Parlee, 1973).

2. Phase scores as an independent variable

Where group data has been of central interest, analysis of variance with repeated measures has been used, using phase as an independent variable. The advantage of this is to control for subject heterogeneity by reducing between group variance attributable to subjects (Keppel 1973). The disadvantage of this design is the risk of carry over effects, which if not of intrinsic interest, must be removed by counter-balancing for order. In menstrual cycle research, this creates problems. One of the only studies to even acknowledge this as a problem, was that of Sanders, Warner, Backstrom, and Bancroft (1983) who systematically varied the day of starting self recording to randomise the effects of repeated measures. By varying the first phase responded to this goes part way towards a solution, however little can be done to vary the order in which cycle phases follow each other. The other limitation arises from the design being limited to group data. Given the difficulties involved with

selecting a homogeneous group, a case is made for the analysis of the individual case. In this, analysis of variance ceases to be of value because of carry over effects and the strong possibility of autocorrelation.

3. sine wave fitting.

The most sophisticated attempt at estabilishing cyclicity has used a least square regression technique to fit one sine wave to one cycle (Sampson & Jenner, 1977). However, if some of the other methodological problems are dealt with by, for example, daily recording, then it is highly likely that the data will be autocorrelated (Jones, Vaught & Weinrott, 1977) and that the pattern of cyclicity will be more complex than one simple frequency with fixed period and amplitude (Kruse & Gottman, 1982). If more than one cycle is examined then this latter point becomes more acute. These cycles are likely to be probabilistic, vaying in period and amplitude, rather than deterministic (Kruse & Gottman 1982). The direct result of this is that the degree of fit worsens over time. Assessing the degree of fit, also raises a problem. The least squares assumption, that the residuals are uncorrelated, is violated for a probabilistic process. Even moderate autocorrelation in the residuals can seriously bias the test of significance of the regression parameters (Glass, Willson & Gottman, 1975; Padia, 1975; Hibbs, 1974; Porges et al., 1980; Horne, Yang & Ware, 1982; Cook & Campbell, 1979). It is reasonable to question the validity of statistical conclusions if a time series model is not at least considered (Gottman, 1981). These three points reduce the utility of Sampson and Jenner's work.

The number of cycles with negative symptoms in the premenstrual phase, required to overcome the problem of

random occurance, remains unspecified. If one assumes equal probability of symptoms or no symptoms, conditional probabilities of symptoms given PMS (p=1.0), and symptoms without PMS (p=0.5), then, from a Bayesian view six cycles are needed to approach p=0.01. At best these assumptions are debatable, but they illustrate the problem. Some defence of the length of data collection is required, rather than the cavalier attitude that tends to prevail.

4-5 SUMMARY

To summarise, the area is plagued with methodological problems, some of which it shares with other areas of research, such as sample representativeness, description of sample in terms that facilitate replication, definition of the syndrome, lack of controls, shortness of intervention phase, and lack of follow-up data. The major methodological limitations that are specific to PMS involve the issues of baseline, prospective recording of symptoms, determination of severity, and consistency of symptom expression. In other words they include those aspects critically related to time as a dimension of the disorder, and the resulting implications for the type of data collected.

SECTION TWO - THE EXPERIMENT

CHAPTER FIVE - OVERVIEW OF THE EXPERIMENT

5-1 INTRODUCTION

The major issues in the PMS field are, (1) how best to identify subjects, (2) how best to collect accurate data, (3) how to decrease the infuence of negative expectation, and (4) the choice of the best form of analysis if prospective data have been collected. Once these issues have been adequately addressed, management regimes can be evaluated.

5-2 SUBJECT IDENTIFICATION

Of the available subject selection instruments, the Steiner scales (Steiner et al. 1980) were used. These scales depend upon sophisticated retrospective judgments. The adequacy of this method of subject selection was compared with prospectively collected symptom data.

5-3 METHOD OF DATA COLLECTION

The disadvantages of retrospective data collection have been reviewed in chapter 4. In summary, some evidence suggests that diagnostic procedures based on retrospective self-report overestimate the condition (McCance et al. 1937; May, 1976; Abplanalp et al. 1979; Sampson & Prescott, 1981; Osborne, 1981; Halbreich, Endicott, Schact & Nee, 1982; Endicott & Halbreich, 1982; Slade, 1984). Direct comparison between prospectively and retrospectively determined incidence and severity, is not possible, as the studies frequently present insufficient data. This comparison was one aim of the experiment.

A direct consequence of this aim, was the need for a

prospective measurement device which satisfied the following requirements. (1) to be minimally intrusive, in contrast to studies using invasive (Sampson & Prescott, 1981), or intensive (Taylor, 1979) styles of prospective data collection; (2) ease and rapidity of use, requiring minimal subject motivation; (3) to have bipolar mood scales (Mackay, 1980), with positive and negative statments in contrast to devices that only present negatively worded statements for endorsement (Steiner et al., 1980; Moos, 1968); (4) to have alternating positive and negative poles to reduce response bias; (5) that cover a range of mood and physical symptoms. No existing questionnaire meets these requirements, but a combination of Visual Analogue Scales for mood (Aitken, 1969; Zeally & Aitken, 1969; Bond & Lader, 1974; Mackay, 1980), and discontinuous rating scales for physical symptoms, has this potential.

A daily diary was constructed incorporating the above features (appendix 1), with instructions for the subject to rate the previous day. Additional information, such as weight, onset of menstruation, and any medication taken was also included. As such the diary had five parts: (1) a general introductory section for the recording of the subject's name, and weight, the date, and if any medication had been taken; (2) eight bipolar VAS scales designed to measure mood symptoms; (3) three yes/no questions concerning menstruation; (4) five physical symptom questions rated absent, mild, severe; (5) an open section for subjects to comment more generally.

The dimensions contained within the symptom scales were derived from the general clinical manifestations literature and the clinical features contained within the RDC proposed

by Steiner et al., (1980) and the associated rating scales. There were some semantic differences between Steiner et al., (1980) and the daily questionnaire, because of the need for superordinate constructs that were able to subsume both negative and positive poles.

Content validity of the physical symptom scales was determined by their overlap with existing scales. The mood VAS were cross-validated against the Multiple Affect Adjective Checklist (MAACL) (Zuckerman & Lubin, 1965), an established and valid mood questionnaire (Mackay, 1980). The results of this study are presented below.

5-3-1 Mood VAS Validation.

The critical validity questions are twofold, given the nature of the prospective nature of the experiment, namely (1) are the two questionnaires significantly correlated when given at the same time? (2) are mood changes, measured by repeated use of both instruments over time, significantly correlated (Johnson & Hackmann, 1977)?

Twenty two females (mean age = 31.1 years, sd = 10.9 years) recruited from hospital staff and a counselling centre, completed the mood VAS, and the MAACL, daily, rating the previous day, for a total of 625 days (mean = 28.4 days, sd = 5.1 days). Correlations for the 22 first pairs, the 22 sets of repeated observations on the mood VAS, and MAACL, and all pairs, are presented in table 5-1.

TABLE 5-1
Means, standard deviations, and correlations between visual analogue mood scale scores and Multiple Affect Adjective Checklist scores

Subject	N	mean		SD		Correlation	Prob
		VAS	MAACL	VAS	MAACL		
1	22	407	38.7	94.2	2.41	-0.5577	<0.01
2	29	402	34.1	54.8	8.13	-0.6505	<0.001
3	29	395	40.3	53.2	0.77	-0.5895	<0.001
4	29	491	38.8	55.0	2.06	-0.3748	<0.05
5	7	351	30.6	59.3	10.24	-0.7577	<0.02
6	30	404	38.3	47.8	2.68	-0.8402	<0.001
7	30	378	38.5	52.2	3.05	-0.5742	<0.001
8	31	530	35.0	97.4	3.60	-0.8512	<0.001
9	31	409	40.1	85.7	1.34	-0.7967	<0.001
10	29	341	43.4	47 4	3.08	-0.6571	<0.001
11	28	509	33.8	50.2	5.83	-0.4709	<0.01
12	30	465	38.7	91.0	3.15	-0.5647	<0.001
13	30	357	47.1	51.9	9.53	-0.7439	<0.001
14	30	425	38.8	77.3	3.37	-0.8121	<0.001
15	26	388	37.9	94.5	5.78	-0.6666	<0.001
16	31	453	19	90.6	8.13	-0.8217	<0.001
17	30	446	32.2	90.8	8.35	-0.7921	<0.001
18	31	486	38.2	78.0	3.52	-0.4791	<0.01
19	30	411	34.8	68.1	5.44	-0.8941	<0.001
20	31	390	37.1	57.1	6.56	-0.5860	<0.001
21	30	500	27.2	94.4	8.61	-0.8520	<0.001
22	31	409	34.9	46.1	3.48	-0.1725	NS
all cases	627	428	36.4	87.7	7.81	-0.5385	<0.001
first pairs	22	417	36.2	98.2	8.64	-0.6091	<0.001

These results, particularly those for first pairs for all subjects, supported the use of the mood VAS as a concurrently valid measuring device.

5-4 NEGATIVE EXPECTATION

Negative beliefs or expectations about symptoms does alter the perception of premenstrual events (Parlee, 1974; Beumont, Richards & Gelder, 1975; Koeske & Koeske, 1973; Ruble, 1977; Englander-Golden, Whitmore & Dienstbier, 1978; Campos & Thurow, 1978; Rodin, 1976; Ruble & Brooks-Gunn, 1979; Abplanalp, Haskett & Rose, 1980; Sherif, 1980; Slade, 1984). Removing the effect of these negative expectations is difficult. Previously suggested means of removal lack utility in a prospective study. It is possible to use of subjects

with PMS who undergo hysterectomy (Osborn, 1981). The absence of menstruation with an intact hormonal substrate allows the experimenter to systematically falsify feedback about cycle phase. The small numbers available, the debate over continued symptoms in this group (Backstrom et al., 1981; Beumont et al., 1975), and possible confounding induced by post-operative trauma, reduce the utility of this option. False assignment of premenstrual subjects to either intermenstrual or premenstrual groups, using electrodes placed upon the subjects head to convince them of the experimenter's ability to predict menstruation onset (Ruble, 1977), is not suitable where data is collected daily over cycles.

An alternative strategy is the use of a placebo treatment designed to counter the possible negative expectations. A placebo being any therapy used for its nonspecific psychological effect (Shapiro, 1968). One of the major reasons for using a placebo, is to eliminating bias on the part of the patient or observer (Beecher, 1955). There is inconclusive evidence to support the existence of a placebo effect for both pain and general mood (Ross, & Buckalew, 1983). In part this is a result of the confusion between a change in behaviour compared with an untreated control (ie., placebo effect), and the response which automatically follows the administration of a placebo (ie., placebo response). This semantic confusion, has led to the lack of use of untreated control groups, and hence to difficulties in interpretation.

Placebo effects are known to be mediated by factors such as size, form, and colour of the placebo used (Jacobs, & Nordan, 1979; Buckalew, & Coffield, 1982a, 1982b). For these

reasons a capsule, of conventional size, would be most suitable. Directive suggestion has been indicated as a major ingredient of a placebo effect, with the placebo itself being a tangible focus, or a reason to believe (Buckalew, 1968, 1972). Positive presentation, with the strong statement that the treatment is a novel approach, is likely to be needed in view of the predominately negative expectations generated by the popular press.

5-5 STATISTICAL ANALYSIS

The need for an adequate and robust technique is critical. The use of visual analysis and verbal desription is of low order, characterises an infant science (Gregson 1983) and is inaccurate (Sharpley, 1981). The statistical techniques which have been used to analyse data from PMS studies all have limitations. These are; (1) problems discriminating mid cycle variability from premenstrual variation (O'Brien et al., 1979); (2) sensitivity to autocorrelation (Gottman, 1981); (3) the ability to analyse only one cycle at a time (Sampson & Jenner, 1977); (4) the indirect nature of the determination of cyclicity

A group of statistical techniques that is able to cope with autocorrelated data and probalilistic cycles is time series analysis. While parametric techniques in the time domain such as Box Jenkins autoregressive intergrated moving average (ARIMA) models (Box & Jenkins, 1970), have recently received an increasing share of attention within the psychological literature (eg. Hartmann et al. 1980; Jones et al. 1977; Cook & Campbell 1979; Ballard 1983), of particular relevance to PMS is analysis in the frequency domain (Spectral Anaylsis). This has been used in a biological context (Luce, 1970), and to examine social interaction

(Gottman, 1979), but has been used extensively in other disciplines such as engineering and econometrics (Jenkins & Watts 1968), to decompose variable phenomena into consituent frequencies.

There are two advantages to decomposition in the frequency domain as opposed to the time domain (Porges et al., 1980). Firstly, estimates of spectral density are approximately independent of frequency and so interpretation is easier than with other time series statistics such as sample autocovariance function. Secondly, with many physical problems, the spectrum or variance associated with various frequencies is of direct interest. For these reasons spectral technology seems to have some utility in the analysis of PMS.

Gottman (1981) presents a cogent summary of the development and technical aspects of frequency domain analysis. What follows is a precis of that, together with additional literature where relevant.

Bernoulli, in the eighteenth century (Hawkins, 1970) suggested that a wide class of functions could be approximated using the sums of trigonometric functions. While this notion was rejected, Fourier, in his treatise The Analytic Theory of Heat (1822) used this technique to simulate data using the sums of sines and cosines, and estimating component frequencies, amplitudes and phase relationships. Fourier's work was in fact, partially in error. The resulting mathematical problems have taken over 100 years to overcome (Gottman 1981).

The difficulties, were two fold. Firstly, there was the failure of the periodogram to be a reliable estimate within either the short or medium run, compared to the theoretical derived spectrum. Secondly, there was a conceptual

difficulty, the solution of which underpins "our century's view of physical phenomena" (Gottmann, 1981, p182). Fourier and a number of those preceding and extending his work (such as Whittaker and Robinson (1924)) aimed to discover deterministic patterns which were masked by white noise. The shift to a probabalistic view, the lack of an assumption of fixed frequencies, amplitudes and phases, has been critical. Yule, in 1921, (Gottman, 1981) suggested the terms psuedo-periodic or quasi-periodic were more appropriate than periodic in that the wave-like movements can be represented by a series of harmonic terms, but not by a fixed function.

This progression in the history of the search for periodicity has moved from a position which ignored the external error component of a deterministic process, to models which conceptualise this error as masking white noise, through to viewing this error as an intrinsic part of the process. The end result of this process can be most clearly seen in the multi-component model of any time series, ie. a time series, Xt = trend + deterministic component + stochastic (probabalistic or nondeterministic) component + error (white noise). The aim of time series analysis, is to systematically remove these components, with the ultimate goal being specification of the stochastic element. This applies to both time and frequency domains and describes the general case. However, trend and the presence or absence of a deterministic component can be of intrinsic interest.

Techniques of analysis have to deal with variability in menstrual cycle length as an intrinsic part of the phenomenon. Standardising cycle length involves making unjustified assumptions about the pacing of hormonal events(). An alternative is to restrict the analysis to one

cycle (Sampson & Jenner, 1977), thereby avoiding the problem of rapid attenuation of the fit which is almost certain given the strong possibility of the data being dominated by stochastic rather than deterministic cycles. It also ignores the possibility of chance occurance of symptoms within the premenstruum. This approach does fit within the historical framework (Gottmann, 1981).

In summary, the major development within the Fourier methods has involved the modification of assumptions or models regarding the underlying process. It means the acceptance of the possibility of a stochastic or nondeterministic component rather than a deterministic component plus measurement error plus other noise.

While the almost exclusive focus of this thesis is on frequency domain analysis, this is not meant to imply a separation between the frequency and time domains. Usually analysis in the two domains are treated as if they were unrelated (eg Kratchowill, 1978 ; Horne et al., 1982; Dahlstrom, 1983). The current emphasis is a direct result of a primary interest in periodicity.

The essence of frequency domain analysis is the spectral decomposition theorem. This states that the variance of any time series can be broken down, or represented by, the contributions of the statistically independent oscillations of different frequencies. The process by which this is achieved is the Fourier Transform. The locally available package (BMDP1T, Dixon 1981) uses several algorithms, collectively known as the Fast Fourier Transform (FFT) to rapidly compute the fourier transform at a discrete set of frequencies, known as the fourier frequencies, or over-tone series ($w=k/T$, $k=0,1,2....(T-1)/2$). Thus the spacing or

distance between independent frequencies is a function of the number of points in the series, and the range of frequencies is from zero to 0.5. The latter value, the Nyquist frequency (Gottmann, 1981) is the period of the fastest frequency able to be detected, which is the distance between two time points, ie f=0.5. This assumes equal spacing of observations, thereby implying the larger the number of observations, the finer will be the frequency grid. The fourier transforms are then used to compute the periodogram, which is then smoothed, using a weighted cosine function, to form the spectral density function. This smoothing or averaging process eliminates the instability of the periodogram. This smoothing is possible because the estimates of density are independent at neighbouring frequencies. The shape of the weighting function is one aspect of this stabilisation process, the other is the bandwidth or number of adjacent periodograms included in the smoothing procedure. Wider bandwidths provide more stable estimates but result in a loss of detail or resolution. As a consequence, this dilemma, Grenander's Uncertainty Principle (Priestly, 1981), is an important consideration in experimental design.

To summarise, the end result is the spectral density function which measures the power or variance on these independent frequencies, namely the overtone series. Trends, or non-stationarity, are shown by peaks at f=0 (infinitely long cycles), deterministic cycles are shown by narrow peaks or line spectra, stochastic or probabalistic cycles by broader peaks, and white noise or random fluctuation by a horizontal line across all frequencies.

The above describes the univariate case. Generalisation to the bivariate case involves two additional statistics.

They are (1) coherence, which is the best linear relationship between the two series at each frequency, and (2) phase, which decribes the temporal relationship between the two series, at each frequency. Coherence is interpretable provided at least some of the power or density is present at that frequency in both of the individual spectral density functions. If the coherence is high at a particular frequency but spectral density is low, the linear relationship is likely to be trivial. The converse is similarly not of interest, since coincidental peaks on the individual spectral density functions are likely to be a function of autocorrelation within each series rather than a reflection of a linear relationship between the series.. Phase is only interpretable if the coherence is significant, because the variance of the phase estimate increases dramatically as coherence approaches zero. The value of the phase estimate, divided by $2\pi f$, is used to estimate the displacement existing between the two series. If this ratio is zero, then the two series, at this frequency, are in phase and synchronous. The slope of the phase over the range of significant coherence, can (dividing by 2π) be used to examine the response time between the two series. A negative slope indicates the two series to be out of phase with the first series leading, and a positive slope suggests the second series leads.

5-6 AIMS OF THE EXPERIMENT

In light of the above, this study aimed to recruite a reasonably homogeneous sample of PMS sufferers, assess them with the retrospective Steiner et al., (1980) scales and two visual analogue severity scales, and prospectively collect symptom data over a sufficiently long period to enable

spectral analysis to be used. Following this, to use a placebo preparation, to modify negative expectations.

The specific aims were: -

(1) to compare retrospective diagnosis, with prospectively determined incidence and severity, and compare difference, phase, and standard scores as ways of summarising these data, while indirectly establishing cyclicity.

(2) evaluate the use of a placebo as a means of altering negative expectancies.

(3) investigate the use of time series analysis, as a means of analysing prospectively collected data.

CHAPTER SIX - STUDY ONE

6-1 INTRODUCTION

The aim of the study reported in this chapter was to directly compare retrospectively and prospectively collected symptom records. The few studies that have addressed this issue have used questionnaires not specifically designed for PMS (Abplanalp et al. 1979), have used normal women (May, 1976), or have presented insufficient detail about the daily questionnaire and the method of analysis (Endicott & Halbreich, 1982). Thus a direct comparison of retrospective initial self-evaluation, and subsequent incidence and severity of the disorder is needed.

The aims were threefold.

(1) To compare retrospective evaluation, using the Steiner scales (Steiner et al. 1980), with prospectively determined incidence and severity.

(2) Within this first aim, to compare the utility of conventional methods of determining cyclicity, such as difference scores, using cycle phase as an independent variable, and the use of standardised scores which enable comparisons across type of symptom.

(3) To examine the ability of a combination of retrospective evaluation devices (specifically the Steiner scales and two visual analogue severity scales) to predict prospectively collected symptom records.

6-2 METHOD

Subjects

Forty two women were finally involved in this study.

They were all of European origin, aged 25-46 years (mean ± sd, 35.06 ± 4.78 years), and were convinced they suffered from PMS. None had overt signs of physical illness apart from transient infections and minor allergies. Those with a psychiatric history or undergoing current and traumatic life experiences were not accepted. None took oestrogen preparations either during the period of observation or in the preceding 3 months, and all had a history of regular menstrual cyclicity. None had been pregnant during the last 1.5 years, nor had lactated in the preceding 12 months. Body weights ranged from 84 to 169% of ideal (Metropolitain Life Insurance, 1959), (mean ± sd, 109.45 ± 15.96), and their numbers of children ranged from 0 to 7 (mean ± sd, 1.67 ± 1.49).

In response to lectures, public notices, newspaper articles, and word of mouth, 58 women were initially recruited. Of these, three were excluded on the basis of taking various medications (despite questioning about this at initial telephone interview) two because of the presence of a major affective disorder, and one because of chronic physical ill health. Of the remaining 52 volunteers, 10 failed to complete recording for the required three months, one because she developed significant physical ill health, the remaining nine because of difficulties with completing the daily diaries on a regular basis.

Procedure

Subjects were interviewed during the luteal phase at which time retrospective rating scales were used to assess severity of current and past symptoms. They began prospective daily recording at the beginning of the next menstrual cycle, and continued for the next three cycles. The daily

questionnaire was completed each morning, rating the previous day. Once completed, subjects were asked to seal it in an envelope. These questionnaires and one early morning urine sample were collected weekly.

Measures

Interview: A 36 item self-rating scale (appendix 2), and 10 item observer rating scale (appendix 3) were used, (Steiner et al., 1980). These scales, covering the day of interview and the previous week, sample both physical and psychological symptoms. Two VAS (Mackay, 1980) were also used, to obtain severity ratings for both the preceding menstrual cycle and the preceding six cycles.

Daily Diary: this instrument (appendix 1) had three major aspects:-

a) Moods were recorded on seven, bipolar 100mm VAS, with the following anchors; happy/unhappy, exhausted/energetic, selfconfident/hopeless, tense/calm, friendly/hostile, confused/mentally alert, efficient/inefficient. Maximum negative mood was scored 0, and the seven scales were summed to give a daily mood score. Rationale for item selection, and concurrent validity with the MAACL (Zuckerman and Lubin, 1965) were presented in chapter five. An eighth VAS was used to rate increases or decreases in sexual interest.

b) Physical symptoms, (headaches, breast-tenderness, constipation, food cravings, bloated feelings) were recorded as absent (0), mild (1), or moderate to severe (2). These were summed daily to give a physical symptom score.

c) General information was also elicited such as whether menstruating, any pain associated with bleeding,

weight, and if any medication had been taken. The latter was used as a check for contaminating drugs such as oral contraceptives, and for the existence of other than trivial health problems.

Urine samples: Each woman collected an early morning sample of urine, once a week, for the estimation of pregnanediol excretion. Ovulation was assumed to have occured if in the 12 days preceding menstruation the 24hr pregnanediol output had exceeded 5 µmol on a single occasion, or if in the same period the total excreted on two occasions, one week apart was > 7 µmol (Metcalf, 1979)

Independent variables

In order to achieve the first aim, that of comparing Steiner retrospective evaluation with prospectively collected data, equal size groups were established using the mean of the two scores obtained on these scales at the interview. These were designated severe (group 1), moderate (group 2) and mild (group 3). The following percentage cut off points were used; group 1 > 66%, 53% < group 2 < 66%, group 3 < 53%.

The second aim required two further independent variables. (1) Phase: The mid-cycle phase was defined as being menstrual days 5-14, day 0 being the onset of menstrual bleeding. The Premenstrual phase was defined as the 5 days preceding the onset of bleeding.

(2) Standardised scores, with mean = 5 and standard deviation = 1, were calculated to enable direct comparisons to be made between the types of symptoms (mode of expression).

The fifth independent variable was cycles, since recording extended over three months.

Dependent Variables

In order to facilitate comparisons and focus upon change in severity rather than absolute level (Rubinow & Roy-Bryne, 1984) the following classes of summary scores, or dependent variables were used:

a) Incidence. To exclude trivial change between the mid-cycle mean score and the premenstrual mean score, an arbitrary 10% change between the two phases was required. In order for PMS to be considered present in a cycle, a difference of 70 is required for daily mood scores, and a difference of 1 for daily physical symptom score.

b) Severity indices. As noted, three methods of summarising the data were used to examine severity. All of these took scores from menstrual days 5-14 as a baseline and compared these to the 5 days preceding the onset of bleeding. These three methods were:

1. difference scores.
   i. Mood. The difference between the mean daily mood score during the last 5 days of the menstrual cycle and the mean for days 5-14.
   ii. Physical symptoms. This was calculated in the same way as the mood difference score.
2. phase scores.
   i. Mood. The mean score for the daily mood ratings of each period (mid-cycle, and premenstrual phase) was analysed.
   ii. Physical symptoms. This was calculated in the same fashion as mood phase score.
3. Standardised scores.
   Both the mood and physical symptom mean scores were standardised across the 42 subjects (x=5,

sd=1), and difference scores calculated as above.

6-3 Results

Out of the 126 cycles studied 2.4% (3 cycles) were annovulatory according to the criteria mentioned above (Metcalf, 1979) and urine samples were unavailable at times critical to the determination of cycle status in 3.9% (5 cycles). The aim was to minimise rather than exclude annovulatroy cycles and thus these were included in the analysis.

The results for this study will be presented in three sections. The first, using analysis of variance (ANOVA), will present results concerning the variability in prospectively determined incidence, in the light of group membership. The second will present an analysis of prospectively measured symptom severity (difference, phase, and standardised), in the light of group membership. The third section, using canonical correlation, will present results relevant to the predictive relationship between retrospective interview scores and prospectively measured symptoms. The eighth VAS, rating increase or decrease in sexual interest was not included in the daily total. Scores on this dimension were, with hindsight, considered to reflect change rather than absolute level, and therefore were inappropriate. All analyses were run on a Burroughs B6900, using BMDP (Dixon, 1981) software.

6-3-1 Incidence:

In the first instance, incidence was determined separately for mood and physical symptoms. The analysis of variance of the number of cycles in which PMS was observed, suggests that there were no significant differences in incidence between groups, or between types of symptoms (table

6-1). Mean incidence (SD) for mood and physical symptoms respectively, were 1.95 (1.0) and 2.07 (0.99) cycles out of a possible 3. Group means (SD) were 2.14 (0.83), 2.25 (0.83), 1.64 (1.17) respectively for groups 1 (severe), 2 (moderate), and 3 (mild) as rated on the Steiner scales.

Table 6-1

ANOVA SUMMARY. Incidence over three months, across groups and mode.

SOURCE	SS	df	MS	F	P
group	5.881	2	2.941	2.22	NS
error	51.607	39	1.323		
mode	0.298	1	0.298	0.53	NS
mode*group	3.167	2	1.583	2.80	NS
error	22.036	39	0.565		

An alternative way of defining incidence is to collapse across symptom type, such that PMS is defined as existing within a cycle provided at least one type of symptom exceeds the criteria of 10% change. The analysis of variance in this case suggests there is no significant variation between groups (table 6-2). Mean incidence (SD) for groups 1 (severe), 2 (moderate), 3 (mild), respectively were 2.5 (0.5), 2.57 (0.62), and 2.21 (1.01).

Table 6-2

ANOVA SUMMARY. Incidence over three months, across groups, collapsed across mode.

SOURCE	SS	df	MS	F	P
group	1.476	2	0.738	1.08	NS
error	26.643	39	0.638		

6-3-2 Severity

A. Difference scores

i. Mood

Analysis of mood difference scores, with group membership and order (month 1, 2, and 3) as independent variables, suggests that while mood scores do not vary significantly across cycles, they do vary significantly across groups (table 6-3). There is no significant interaction between group membership and order.

Table 6-3

ANOVA SUMMARY. mood difference scores

SOURCE	SS	df	MS	F	P
group	207327	2	103663	3.44	0.04
error	1174955	39	30127		
cycle	24087	2	12043	1.44	NS
group*cycle	37661	4	9415	1.22	NS
error	654536	78	8391		

Mean scores across groups show a decreasing trend in mood difference scores from group 1 (severe), with a mean score (sd) of 173 (164), group 2 (moderate), with a mean (sd) of 109 (100), to group 3 (mild), with a mean (sd) of 77 (88). The decreasing trend in mean difference scores is consistent with decreasing retrospectively rated severity across groups.

ii. Physical

Analysis of variance (table 6-4) suggests that physical symptom difference scores are not significantly different between cycles (order main effect), nor across groups (group main effect). The interaction between group membership and order approaches significance ($p=0.0506$) suggesting that for

each group physical symptoms varies differently across cycles. Mean difference scores for each group across cycles suggest group 1 (severe) becomes less affected over the three cycles, with mean difference scores (sd) of 1.96 (1.32), 2.15 (1.55), and 1.24 (1.50) respectively. Group 2 (moderate), increases in severity with scores of 1.87 (1.22), 2.23 (1.65), and 2.15 (0.93), while group 3 (mild) fluctuates, with scores of 1.81 (1.79), 1.26 (1.27), and 1.80 (1.36) for cycle 1, 2, and 3 respectively.

TABLE 6-4

ANOVA SUMMARY. physical difference scores

SOURCE	SS	df	MS	F	P
groups	5.90	2	2.951	0.68	NS
error	168.14	39	4.311		
cycles	0.40	2	0.202	0.18	NS
group*cycle	10.85	4	2.713	2.48	0.05
error	85.29	78	1.093		

B Phase scores

i. Mood

Mood scores are significantly different across phases (table 6-5). Mean scores are in the expected direction, with lower mood in the premenstrual phase, phase 2 (mean score (sd) 339 (108)), compared to 460 (75) in phase 1 (mid-cycle). The mean mood score (sd), collapsed across cycles and phases, for each group, 382 (140), 387 (94), and 430 (87) respectively for groups 1, 2, and 3, approaches significance (p=0.07), and show the expected increasing trend, reflecting decreasing severity, from group 1 to group 3. There is no

significant variation across cycles (order main effect).

Table 6-5

ANOVA SUMMARY mood scores by group, cycle and phase

SOURCE	SS	df	MS	F	P
group	1155.9	2	577.9	2.87	0.07
error	7850.7	39	201.3		
cycle	3.6	2	1.8	0.06	NS
cycle*group	203.3	4	50.8	1.72	NS
error	2035.9	78	29.6		
phase	9142.9	1	9124.6	63.1	0.00
group*phase	1060.8	2	530.4	3.66	0.03
error	5649.1	39	144.9		
phase*cycle	149.2	2	74.6	1.77	NS
group*phase*cycle	201.7	4	50 4	1.19	NS
error	3294.5	78	42.24		

Of the interactions, only groups*phases achieved significance. Mean scores show consistency across groups for mean mid-cycle (phase 1) mood scores; 470 (93), 442 (57), and 468 (68) for groups 1, 2, and 3 respectively. There was an increasing trend for mean premenstrual (phase 2) mood scores (sd), from group 1 (severe) to group 3 (mild); 294 (119), 332 (93) and 391 (87) respectively for groups 1, 2, and 3. This suggests that the group main effect from scores collapsed across phases is almost entirely a function of variation across groups in premenstrual scores. This highlights the advantage of phase scores over difference scores (table 6-3) where group variance significant but not able to be analysed according to phase. However the two sets of results are

consistent.

ii Physical

As for mood scores, the variation in scores between phases is significant (table 6-6) and mean scores again show a greater severity of symptoms premenstrually as opposed to mid-cycle, with mean scores (sd) being 0.32 (0.50), and 2.15 (1.42) respectively. Similarly, variation in physical symptoms across cycles is not significant but, in contrast, scores do not vary significantly between groups despite an observable decrease in mean score from group 1 to group 3; mean score (sd) being 1.37 (1.46), 1.33 (1.40), and 1.02 (1.34) respectively for groups 1, 2, and 3.

Table 6-6

ANOVA SUMMARY Physical symptom scores by groups cycles and phases

SOURCE	SS	df	MS	F	P
group	6.08	2	3.04	1.02	NS
error	115.83	39	2.97		
cycle	0.83	2	0.41	1.11	NS
cycle*group	0.33	4	0.08	0.22	NS
error	29.07	78	0.37		
phase	210.29	1	210.29	99.2	0.00
group*phase	2.47	2	1.24	0.58	NS
error	82.67	39	2.12		
phase*cycle	0.45	2	0.23	0.41	NS
group*cycle*phase	4.74	4	1.19	2.13	NS
error	43.46	78	0.56		

None of the interactions achieve significance. Of interest, given the mood score analysis, was groups*phases. Mean scores (sd) for phase 1 (mid-cycle) were 0.46 (0.73),

0.29 (0.35), and 0.22 (0.28) respectively for groups 1, 2, and 3. For phase 2 (premenstrual) the mean scores (sd) were 2.28 (1.46), 2.38 (1.46), and 1.82 (1.49) respectively. The nonsignificant interaction reflects mid-cycle variation consistent with group severity, with group 1 having more symptoms, and premenstrual variation which does not reflect group differences in severity. This again is consistent with difference scores (table 6-4) and shows the advantage of phase scores.

C. STANDARDISED DIFFERENCE SCORES

The standardised data showed no significant variation between groups, symptom type nor cycles.

Table 6-7

ANOVA SUMMARY standard scores across group, cycle and mode

SOURCE	SS	df	MS	F	P
group	85866	2	42933	1.59	NS
error	1055197	39	27056		
cycle	12592	2	6296	0.80	NS
cycle*group	73317	4	18329	2.33	NS
error	612856	78	7857		
mode	364	1	364	0.03	NS
group*mode	71290	2	35645	2.84	NS
error	490186	39	12568		
cycle*mode	9299	2	4649	1.64	NS
group*cycle*mode	4028	4	1007	0.36	NS
error	220643	78	2828		

6-3-3 Interview data

Canonical correlation was used an alternative to analysis of variance, as a means of examining the

relationship between retrospective ratings of symptoms at interview, and the prospectively recorded symptoms. As such the predictor variables or first set, were scores on the interview measures; (1) self rating scale (SRS), (2) observer rating scale (ORS), (3) a VAS rating severity of symptoms of the previous 1 month (VAS1), and (4) a VAS rating severity over the previous 6 months (VAS6). Variables in the second or criterion set, were the mood and physical symptom difference scores for the three months of recording, making six variables in all. All analyses were carried out using BMDP6M (Dixon, 1981).

Canonical Correlations

Canonical correlations are presented in table 6-8, along with eigenvalues associated with each pair of canonical variates. Only the first pair of canonical variates are significant. The two sets of variables overlap significantly, with the first pair of canonical variates accounting for 45.6% of the variance involved.

Table 6-8

EIGENVALUE	CANONICAL CORRELATION	NUMBER OF EIGENVALUES	BARTLETT'S TEST FOR REMAINING EIGENVALUES		
			CHI-SQUARE	DF	PROB
			37.00	24	0.0438
0.45574	0.67509	1	14.19	15	0.5114
0.16710	0.40878	2	7.33	8	0.5015
0.12614	0.35517	3	2.27	3	0.5177
0.05882	0.24253				

To facilitate description of this first canonical correlation (Neufeld 1977), the correlation between it and the original variables are presented in table 6-9.

The canonical variable loadings for the first set

were described primarily, by the 1 month visual analogue scale, and to a lesser degree by the two Steiner rating scales. The canonical variable loading for the second set, were best described by physical symptoms (cycle 2) and mood (cycle 2), and to a lesser extent by mood in both cycle 1 and 3.

Table 6-9

	Canonical variable loadings
SET 1	
Canonical Correlation	1
Self Rating Scale	0.591
Observer Rating Scale	0.532
Visual Analogue Scale (1 month)	0.923
Visual Analogue Scale (6 months)	0.288
SET 2	
Canonical Correlation	1
mood symptoms, cycle 1	0.338
physical symptoms, cycle 1	0.142
mood symptoms, cycle 2	0.623
physical symptoms, cycle 2	0.804
mood symptoms, cycle 3	0.319
physical symptoms, cycle 3	0.014

Multiple correlations

i. Within Sets

There was a low multiple correlation between VAS1 and the other variables in set one (table 6-10). The strong linkage found in the first canonical correlation, between this variable and the second set, suggests it is measuring a different but useful dimension, compared to the other predictor variables. The strong relationship between the two

Steiner scales is expected in that they contain essentially the same items presented in a different format, and rated by different people. However their involvement in the first canonical correlation linking the two sets is moderate.

Table 6-10

Squared Multiple Correlations for each variable in the first set with all other variables in the first set

variable	R2
self rating scale	0.654
observer rating scale	0.660
visual analogue scale 1month	0.182
visual analogue scale 6month	0.204

For variables within the second set, the multiple correlations (table 6-11), suggest there is a moderate relationship between the various symptom measures taken over time. This is consistent with the ANOVA results presented in the previous section.

Table 6-11

Squared Multiple Correlations for each variable in the second set with others in the second set

variable	R2
mood symptoms (cycle 1)	0.498
physical symptoms (cycle 1)	0.607
mood symptoms (cycle 2)	0.575
physical symptoms (cycle 2)	0.508
mood symptoms (cycle 3)	0.588
physical symptoms (cycle 3)	0.464

ii Between Sets

The multiple correlations between variables in the first

set and all variables in the second set (table 6-12), are consistent with the canonical correlations. The only multiple correlation to achieve significance was that associated with VAS1.

Table 6-12

Squared Multiple correlations for each variable in the first set with all variables in the second set

variable	R2	F	df	P
self rating scale	0.262	2.19	6 37	0.089
observer rating scale	0.240	1.94	6 37	0.124
visual analogue scale 1 month	0.408	4.26	6 37	0.006
visual analogue scale 6 month	0.119	0.83	6 37	0.513

The multiple correlations between variables in the second set with all variables in the first set (table 6-13), are also consistent with the information given by the first canonical correlation. The only significant correlations are mood and physical symptoms in cycle 2. The combined battery of interview scales are only able to predict one out of the three months, and this to a limited degree (25% and 31% of the criterion variance for mood and physical symptoms respectively).

Table 6-13

Squared Multiple correlations for each variable in the second set with all variables in the first set

variable	R2	F		df	P
mood (cycle 1)	0.070	0.73	4	39	0.575
physical symptom (cycle 1)	0.074	0.78	4	39	0.546
mood (cycle 2)	0.245	3.17	4	39	0.024
physical symptoms (cycle 2)	0.308	4.35	4	39	0.005
mood (cycle 3)	0.144	1.64	4	39	0.184
physical symptoms (cycle 3)	0.002	0.02	4	39	0.999

redundancy index.

An estimate of the proportion of the variance in one set that is related to variation in the other, namely the redundancy index, was obtained for the one significant canonical correlation. This index is 0.18 for the first set, and 0.10 for the second set. The overlap between the two sets of variables therefore accounts for only a minor proportion of the variation within each set.

6-4 Discussion

The low rate of annovulatory cycles avoids rather than confronts the controversy about the presence of PMS in such cycles. This however reflects a relatively homogeneous group.

6-4-1 Incidence

The lack of any significant variation, for any of the independent variables supports the hypothesis that retrospective rating is inadequate. However, groups were constituted on the basis of retrospective, self-reported severity of symptoms. This result may therefore be a function of inadequate assessment.

It does however suggest that retrospective self-rated

severity is an inadequate guide to incidence. Consistency of symptoms is seldom reported, and appears to be inferred from severity. It is interesting that even using the most lenient criteria for a positive cycle, none of the groups showed totally consistent presence of PMS. This supports the point that treatment evaluation, using retrospective or prospective recording confined to one or two cycles, is likely to encounter problems. This could be overcome by selecting a subset of subjects with consistent symptom expression.

6-4-2 Severity

In the three approaches to quantifying severity, the lack of any significant cycle variation, suggests that the act of daily recording, does not, reduce symptom severity. This is in contrast to the self-monitering literature which suggests that it is decreased by self-recording. It may well be that the time scale for premenstrual symptoms is so long, that memory difficulties serves to reduce the effect of self-monitering, as well as inhibit the accuracy of retrospective self-report.

Difference scores vary significantly across groups for mood scores but not for physical symptoms. It is not, however, possible to detect whether this variation in mood scores is due to mid-cycle or premenstrual variation.

Phase scores show the expected pattern for both mood and physical symptoms. The differences between phases is significant and the mean scores are less severe at mid-cycle. The significant group variation for mood scores, but not physical symptoms, parallel the results for difference scores. The advantage of using phase as an independent variable lies in the group*phase interaction and the suggestion that the significant variation in mood scores is

premenstrual rather than mid-cycle.

Standardised scores are of little value. There was no significant variation for any of the independent variables. This contrasts to the significant variation found with other summary scores.

In summary, the null hypothesis for this study is supported for physical symptoms since there are no significant differences between groups in severity of these symptoms. This was not so for mood where significant differences existed. These were in the expected direction. The most useful style of summary score appears to be that which treats mid-cycle and premenstrual scores independently.

6-4-3 Interview

The results of the canonical correlation analysis suggests the following.

(1) While the first canonical correlation accounts for a significant proportion of the overlap variance (45.6%), the redundancy index suggests the degree of overlap is relatively small (18% for set one, and 10% for set two). The VAS1 was the most powerful predictor of subsequent symptoms followed by the two Steiner scales. The VAS6 was least predictive.

(2) The low multiple correlation between VAS1 and the other variables in set 1, together with its strong linkage in the first canonical correlation, suggests it is measuring a different but useful dimension. Its simplicity confers an added advantage. The consistency of symptoms across months supports the lack of order effects found in the analysis of variance.

(3) The multiple correlations between sets are consistent with the canonical correlation analysis in that only VAS1 correlates significantly with symptoms.

6-4-4 Summary

Groups discriminated on the basis of retrospective self-reported symptom severity do vary significantly with respect to prospectively recorded mood symptoms, but not with respect to physical symptoms or incidence. Phase related symptom scores are the most useful type of summary score, although difference scores have the advantage of being expressed as a single number.

The amount of overlapping variance between the retrospective ratings and prospectively recorded symptoms is small, but is best predicted by a simple VAS rating symptom severity over the previous month.

CHAPTER SEVEN - STUDY TWO

7-1 Introduction.

The study reported in this chapter aimed to investigate negative expectancies, or beliefs, known to affect the perception of premenstrual events (Ruble & Brooks-Gunn, 1979). Previous attempts to modify expectancies have limitations, especially for prospective trials. This study attempted to negate these beliefs, if they existed, by inducing treatment expectations by way of a placebo. A placebo effect is by definition nonspecific (Shapiro, 1968), but it may be used to reduce patient and observer bias (Beecher, 1955). This is usually in the context of evaluating an active treatment, but in this case the placebo effect is of primary interest, rather than a means of experimental control.

The specific aims were threefold.

(1) to evaluate the effect of a placebo on prospectively determined incidence and symptom severity.

(2) to use the Steiner scales (Steiner et al., 1980) to compare retrospective evaluation before and after placebo, with prospective determined incidence and severity.

(3) to examine the ability of the combination of retrospective evaluation devices, before and after placebo, to predict prospectively collected symptom records.

(4) to examine the relationship between interview evaluations on the three occassions.

7-2 Method

Subjects

Thirty subjects from the first study agreed to continue for an additional three months. Of the 12 who withdrew, 9 did so before begining this study. Reasons were: (a) medical, including a desire to take other medication (4 S's); (b) daily recording too time consuming (3 S's); (c) going on holiday (2 S's). Two subjects recorded insufficient data, and one felt that the placebo medication was generating an unacceptable level of constipation. These women continued to meet the inclusion criteria detailed for Study 1, and had very similar ages, weights and numbers of children; Age (mean ± sd, 35.14 years ± 4.8 years), weight (mean percentage of ideal body weight, ± sd, 110.6% ± 16.18%), number of children (mean ± sd 1.64 ± 1.49).

Procedure and Measures

Using the same measures as in the initial interview (interview 1), subjects were reinterviewed during the luteal phase of the third cycle of study 1. This was labelled interview two. The daily measuring device was the same as that used in study 1. Eleven subjects were persuaded to delay begining the placebo treatment for one cycle, as an attempt to control for continued recording resulting in a significant reduction in incidence and severity of symptoms. Ideally, a randomly selected subgroup would have just recorded daily symptoms over the three months to provide this control. This was not possible as the effort involved and the inability to seek treatment while recording, created some difficulties with subject compliance. The lack of significant variation across cycles found in study 1 made sudden improvement unlikely.

All subjects were interviewed again during the luteal phase of their sixth cycle, or seventh for those with the extra month's recording (interview 3). Additional information gathered at this final interview, were VAS scores, rating treatment effectiveness and severity of symptoms for the preceeding three treated cycles (appendix 4).

A placebo capsule containing 0.1mg Priydoxine (5-10% of typical daily intake by diet (Birkbeck,1977)), and 0.75g glucose, was taken daily on arising, from the begining of the fourth or fifth menstrual cycle. Subjects were told the trial was to test the theraputic effectiveness of a novel administration of Pyridoxine and Glucose. No information was given as to the specific composition of the mixture. Written consent forms were obtained from each subject (appendix 7).

Independent Variables

There were four independent variables, three as for study 1, and the additional variable, treatment. Treatment 1 was the three control cycles collected in study 1. Treatment 2 was the three placebo treated cycles. The extra month of recording, for the seven subjects, was not included in the major analyses. The group variable was generated in the same manner as study 1, with three equal size severity classifications based on the two Steiner scales, with group 1 (severe), group 2 (moderate), and group 3 (mild). Phase was defined as for study 1, with the mid-cycle contrast period, phase 1, being menstrual days 5 to 14, and phase 2, the premenstrual phase, ie., the last 5 days preceeding bleeding. The fourth variable, cycles, was the three menstrual months of recording.

Dependent Variables

The same procedures were used to summarise scores for

this study as in study 1. Difference and phase scores used menstrual days 5 to 14 as a contrast to the 5 days preceeding bleeding. Standardised scores, however, were not used given their lack of utility in study 1.

7-3 RESULTS

Out of the 187 cycles studied, 2.2% (4 cycles) were annovulatory (Metcalf, 1979). Urine samples critical to the determination of ovulation, were not provided in 4.4% (8 cycles). The aim was to minimise rather than exclude annovulatory cycles and thus these were included in the analysis.

The results for this study will be presented in four sections.

(1) results concerning variability in incidence in relation to the independent variables group and treatment.

(2) the analysis of severity in response to the independent variables group and treatment, for mood and physical symptoms.

(3) the changes in severity between the third, fourth and fifth month for the two groups of subjects who either began treatment, or continuing recording during the fourth month.

(4) the analyses of the relationships between (a) interview one and interview two, (b) interview two, that preceeding treatment, and subsequent symptom scores, (c) interviews two and three, (d) interview three, following treatment and the prospective symptom records for the preceeding three months, (e) visual analogue ratings of premenstrual distress at interview three, with the symptom records from the three preceeding treated cycles, (f) visual analogue ratings of treatment effectiveness at interview

three, with the symptoms from the treated cycles, (g) a combination of the treatment effectiveness and distress ratings, with the symptoms collected over the three treated months.

7-3-1 Incidence

Incidence was first calculated separately for mood and physical symptoms.

An analysis of variance showed a significant treatment main effect, with incidence decreasing from a mean (sd) of 1.96 (0.99), to 1.5 (1.02) in treated cycles. No significant difference between groups was present, with mean (sd) scores being 1.73 (0.94), 1.95 (0.88), and 1.53 (1.13), for groups 1, 2, and 3 respectively. Similarly, no significant difference was found between types of symptoms, with mean (sd) incidence scores of 1.60 (1.01) cycles and 1.86 (1.03) cycles for psychological and physical modes respectively. The interaction between group and mode of expression was significant, with mean (sd) scores for psychological symptoms over groups 1, 2 and 3 being 1.95 (0.83), 1.80 (0.95), 1.05 (1.05) respectively, and 1.5 (1.10), 2.1 (0.91), 2.0 (1.03) respectively for physical symptoms. None of the other interactions achieved significance (table 7-1).

Table 7-1

ANOVA SUMMARY Incidence, over six months, across treatments, groups, and mode.

SOURCE	SS	df	MS	F	P
group	3.617	2	1.808	1.24	NS
error	39.350	27	1.457		
treatment	6.533	1	6.533	9.56	0.005
error	18.450	27	0.683		
mode	2.133	1	2.133	1.72	NS
mode*group	9.817	2	4.908	3.95	0.031
error	33.550	27	1.243		
treatment*mode	0.533	1	0.533	1.56	NS
treatment*mode*group	1.717	2	0.858	2.51	NS
error	9.250	27	0.343		

Where incidence was determined positive if either psychological or physical symptoms achieved the 10% change criteria, the analysis of variance showed no significant effects (table 7-2).

Table 7-2

ANOVA SUMMARY Incidence over six months, across treatments and groups, collapsed across mode.

SOURCE	SS	df	MS	F	P
group	0.900	2	0.450	0.43	NS
error	28.250	27	1.046		
treatment	0.417	1	0.417	1.14	NS
treatment*group	0.233	2	0.117	0.23	NS
error	9.850	27	0.365		

7-3-2 Severity

A. Difference Scores

i Mood

Analysis of mood difference scores with treatment, group and cycles (order) as independent variables, suggests that while mood scores do not differ significantly across cycles, they do vary significantly across treatments and with group membership (table7-3). None of the interactions were significant.

Table 7-3

ANOVA SUMMARY mood difference scores

SOURCE	SS	df	MS	F	P
group	122903	2	61451	3.48	0.05
error	476121	27	17634		
treatment	91035	1	91035	12.31	0.001
treatment*group	21948	2	10974	1.48	NS
error	199729	27	7397		
cycle	1919	2	960	0.11	NS
cycle*group	23365	4	5841	0.67	NS
error	467784	54	8662		
treatment*cycle	8259	2	4129	0.38	NS
treatment*cycle*group	17450	4	4362	0.40	NS
error	585445	54	10841		

Placebo treatment resulted in a significant decrease in severity of mood difference score. Mean scores (sd) were, 113 (110) for control cycles, and 68 (97) for the placebo cycles. It is not clear whether this reflects mid-cycle and/or premenstrual change. Analysis of phase scores will clarify this.

Mean scores (sd) for groups 1, 2, and 3, were 119 (132), 97 (93), and 56 (80), respectively. The decreasing trend from group 1 to group 3 (severe to mild) is consistent with the results in study 1, and the hypothesis that retrospective reporting meaningfully relates to prospective recording of symptoms. The difficulty in interpreting difference scores makes it unclear whether this trend across groups reflects premenstrual and/or midcycle variation.

ii. Physical

The analysis of variance of physical symptom difference scores across treatments, groups and cycles is similar to that for mood difference scores, except there are no significant differences between groups (table 7-4). None of the interactions were significant

Table 7-4

ANOVA SUMMARY physical symptom difference scores

SOURCE	SS	df	MS	F	P
group	0.454	2	0.2268	0.03	NS
error	183.900	27	6.8111		
treatment	9.987	1	9.9876	9.82	0.004
treatment*group	2.035	2	1.0176	1.00	NS
error	27.464	27	1.0172		
cycle	1.747	2	0.8737	0.84	NS
cycle*group	3.771	4	0.9428	0.90	NS
error	56.411	54	1.0446		
treatment*cycle	0.230	2	0.1153	0.12	NS
treatment*cycle*group	5.862	4	1.4656	1.48	NS
error	53.410	54	0.9890		

Groups differing in retrospectively rated severity do

not differ significantly in mean physical symptom difference scores. Similarly, no significant variation is found between cycles across or within treatments.

Physical symptom difference scores were less severe under placebo. Mean scores (sd) were 1.83 (1.48) and 1.35 (1.25) for control and placebo cycles respectively. Again it is unclear whether mid cycle or premenstrual change is the source.

B Phase Scores

i. Mood

Placebo treatment resulted in a significant increase in positive mood (table 7-5). Mean scores (sd) for control and placebo cycles were 408 (100), and 447 (98.6) respectively. The treatment*phase interaction is significant suggesting that treatment effects vary according to phase. Mean scores (sd) for control cycles were 464 (66.9), and 352 (98.1) for mid-cycle and premenstrual phases respectively, and 482 (78), 412 (104) respectively for the placebo cycles. While placebo treatment does affect mood scores generally, this effect is not significant at mid-cycle compared with the effect upon premenstrual mood. None of the other treatment interactions were significant.

Mood scores varied significantly with phase. Mean mood scores reflected lower mood premenstrually, with mean score (sd) of 382 (105), than at mid-cycle where the mean score (sd) was 473 (73.1). The treatment*phase interaction was discussed above. The phase*group interaction was significant and is discussed in conjunction with the group main effect. None of the other phase interactions were significant.

Mood scores do not differ significantly between groups. However the group*phase is significant. Mean scores (sd) for

mid-cycle were 479 (69), 459 (76), and 481 (73.1) for groups 1, 2 and 3, respectively. For the premenstrual phase, the mean scores (sd) for groups 1, 2 and 3 were 358 (116), 363 (101), and 425 (84.1). This suggests little mid-cycle variation between groups but a positive increase in premenstrual mood from group 1 to group 3 (severe to mild). None of the other group interactions are significant.

The lack of significant variation between cycles within treatments (treatment*cycle interaction), is of interest given the limitations of the design. There is a stable baseline prior to intervention with mean scores (sd) of 408 (101), 408 (105), and 409 (97.6) for control cycles, and a clear increase at the beginning of treatment, with scores of 431 (106), 449 (83.3) and 461 (103) respectively. The transition lends support to the conclusion that improvement is not a function of time alone.

Table 7-5

ANOVA SUMMARY mood score by treatment, group, cycle and phase

SOURCE	SS	df	MS	F	P
group	124550	2	62274	1.61	NS
error	1045471	27	38721		
treatment	140857	1	140857	13.80	0.001
treatment*group	11029	2	5514	0.54	NS
error	275492	27	10203		
cycle	14944	2	7472	2.65	NS
cycle*group	5171	4	1292	0.46	NS
error	152104	54	2816		
phase	742471	1	742471	83.36	0.001
group*phase	66739	2	33369	3.75	0.037
error	240494	27	8907		
treatment*cycle	13035	2	6517	1.86	NS
treatment*cycle*group	9479	4	2369	0.68	NS
error	189051	54	3500		
treatment*phase	40343	1	40343	11.01	0.003
treatment*group*phase	10193	2	5096	1.39	NS
error	98967	27	3665		
cycle*phase	1832	2	916	0.21	NS
cycle*group*phase	12237	4	3059	0.70	NS
error	234769	54	4347		
treatment*cycle*phase	6042	2	3021	0.60	NS
treat*cycle*group*phase	12190	4	3047	0.60	NS
error	272863	54	5053		

ii. Physical Symptoms

Placebo treatment resulted in significantly lower

physical symptom scores (less symptoms) in the placebo condition (table 7-6). Mean scores (sd) were 1.25 (1.43) for control cycles and 1.00 (1.23) for placebo. Treatment was also phase specific, with mid-cycle mean scores (sd) for control and placebo cycles respectively being 0.35 (0.54) and 0.33 (0.45). Premenstrually, again for control and placebo cycles respectively the mean scores (sd) were 2.15 (1.47) and 1.68 (1.39).

Physical symptom score was significantly more severe premenstrually than at mid-cycle (phase main effect). The mid-cycle mean score (sd) was 0.34 (0.49), with a premenstrual score of 1.91 (1.45).

The lack of significant within-treatment variation between cycles in physical symptom scores, is of interest given the possiblity that recording itself may reduce severity. There was an increasing trend in severity prior to intervention with respective mean scores (sd) for the three control cycles of 1.19 (1.45), 1.25 (1.51) and 1.32 (1.34). A substantial decrease was evident during the first month of treatment, with a mean score (sd) of 1.08 (1.24). Subsequent mean scores (sd) for cycles five and six were 0.95 (1.22) and 0.97 (1.26). The suggested trend lends support to the conclusion that improvement is not a function of time alone.

In contrast to mood scores, there were no significant group or group interaction effects.

Table 7-6

ANOVA SUMMARY physical symptom scores across treatment, group, cycle and phase

SOURCE	SS	df	MS	F	P
group	0.135	2	0.07	0.01	NS
error	157.565	27	5.83		
treatment	5.041	1	5.04	4.17	0.051
treatment*group	5.544	2	2.77	2.29	NS
error	32.662	27	1.20		
cycle	0.110	2	0.05	0.15	NS
cycle*group	0.920	4	0.23	0.64	NS
error	19.403	54	0.35		
phase	223.098	1	223.10	67.05	0.001
group*phase	0.367	2	0.18	0.06	NS
error	89.832	27	3.32		
treatment*cycle	0.828	2	0.41	1.05	NS
treatment*cycle*group	0.990	4	0.24	0.63	NS
error	21.318	54	0.39		
treatment*phase	4.096	1	4.10	7.96	0.008
treatment*group*phase	0.996	2	0.49	0.97	NS
error	13.872	27	0.51		
cycle*phase	0.837	2	0.41	0.78	NS
cycle*group*phase	1.918	4	0.48	0.89	NS
error	28.971	54	0.53		
treatment*cycle*phase	0.093	2	0.04	0.09	NS
treat*cycle*group*phase	2.379	4	0.59	1.09	NS
error	29.517	54	0.54		

7-3-3 Fourth Control Month

Eleven subjects agreed to continue recording for an additional cycle. An analysis of variance for cycle 3 and

cycle 4 for mood symptoms (table 7-7) indicates there are no significant differences between cycles. Mean scores (sd) were 411 (59.7) and 429 (67.0) for cycle 3 and 4 respectively. The significant difference between phases was expected given the significant phase main effect found in the ANOVA for mood scores in both control and placebo cycles.

Table 7-7

ANOVA SUMMARY mood scores across phase for cycles three and four (control subjects)

SOURCE	SS	df	MS	F	P
cycles	3636.4	1	3636.4	1.77	NS
error	20531.6	10	2053.2		
phase	160809.1	1	160809.1	14.80	0.003
error	108660.9	10	10866.1		
cycles*phase	44.0	1	44.0	0.02	NS
error	19574.0	10	1957.4		

Physical symptom scores similarly show no significant differences between cycles 3 and 4. Mean scores (sd) were 1.27 (0.79) and 1.27 (1.24) for cycle 3 and 4 respectively. The significant difference between phases was again expected and not central to the aim of this analysis.

Table 7-8

ANOVA SUMMARY physical symptom scores across phase for cycles three and four (control subjects)

SOURCE	SS	df	MS	F	P
cycles	0.0003	1	0.0003	0.00	NS
error	6.0223	10	0.6022		
phase	38.7657	1	38.7657	28.22	0.001
error	13.7368	10	1.3737		
cycles*phase	0.4602	1	0.4602	2.50	NS
error	1.8422	10	0.1842		

A second set of analyses was carried out on the fourth cycle alone. The eleven control subjects were compared to the nineteen subjects who began placebo. Mood scores for this cycle (table 7-9) continued to show a significant difference between phases, but there were no significant differences between control and placebo subjects, nor any strong evidence for a phase specific treatment effect. The treatment*phase interaction however showed a nonsignificant trend ($p=0.144$) which is illustrated by the mean scores (sd). These were 488 (81), and 370 (93) for control subjects over phase 1 and 2 respectively, and 453 (77) and 400 (123) for placebo treated subjects in phases 1 and 2 respectively. These differences were nonsignificant but in the expected direction.

Table 7-9

ANOVA SUMMARY mood scores across phase and treatment (month four)

SOURCE	SS	df	MS	F	P
treatment	98	1	98	0.01	NS
error	346869	28	123888		
phase	103763	1	103763	15.81	0.000
phase*treatment	14819	1	14819	2.26	NS
error	183777	28	6563		

For cycle 4, physical symptom scores are similar to that for mood. A significant difference occured between phases, but neither treatment nor treatment*phase interaction was significant. Mean scores (sd) were 0.44 (0.85) and 2.11 (1.75) for control subjects in phases 1 and 2 respectively, and 0.41 (0.44) and 1.65 (1.11) for placebo treated subjects in phases 1 and 2 respectively. Again this nonsignificant difference is in the expected direction.

Table 7-10

ANOVA SUMMARY physical symptom scores across phase and treatment (cycle 4)

SOURCE	SS	df	MS	F	P
treatment	0.828	1	0.828	0.52	NS
error	44.517	28	1.589		
phase	29.702	1	29.702	44.11	0.001
phase*treatment	0.630	1	0.630	0.94	NS
error	18.855	28	0.674		

7-3-4 Interview Data

7-3-4-1 First and Second Interview

The first and second interview scores were used, to examine the stability of such scores over time. The predictor variables or first set were scores on interview one; (1) self rating scale (SRS(1)), (2) observer rating scale (ORS(1)), (3) visual analogue scale 1 month (VAS1(1)), and (4) visual analogue scale, 6 months (VAS6(1)). Variables in the second set, the criterion set, were score at interview two; (1) SRS(2), (2) ORS(2), (3) VAS1(2), and (4) VAS6(2). All analyses were run on BMDP6M (Dixon, 1981).

i Canonical Correlation

Canonical correlations are presented in table 7-11, along with eigenvalues associated with each pair of canonical variates. The two sets of variables show significant overlap at $p<0.05$. The first pair of canonical variates accounts for 61.3% of the variance that is shared by the two sets of variables. The second pair accounts for 24.2%. The third pair of canonical variates are also significant but accounts for only 3.9%. In total, 89.4% of the overlap variance is described by the first two canonical correlations.

Table 7-11

EIGENVALUE	CANONICAL CORRELATION	NUMBER OF EIGENVALUES	BARTLETT'S TEST FOR REMAINING EIGENVALUES		
			CHI-SQUARE	DF	PROB
			55.16	16	0.0001
0.61318	0.78306	1	20.50	9	0.0151
0.24224	0.49218	2	10.37	4	0.0346
0.03890	0.19723	3	1.45	1	0.2288

To facilitate description of the first two significant

canonical correlations (Neufeld 1977), the correlation between them and the original variables are presented in table 7-12.

Table 7-12

	Canonical variable loadings	
SET 1		
Canonical Correlation	1	2
SRS(1)	0.984	-0.078
ORS(1)	0.865	0.330
VAS1(1)	0.279	-0.527
VAS6(1)	0.409	-0.378
SET 2		
Canonical Correlation	1	2
SRS(2)	0.777	-0.258
ORS(2)	0.897	0.392
VAS1(2)	0.475	-0.387
VAS6(2)	0.543	-0.429

For the first canonical correlation the canonical variable loadings for both sets were described primarily by the Steiner scales. The canonical variable loadings for the other two variables in both sets were moderate. For the second canonical correlation, moderate negative correlations exist between the VAS scales in both sets, moderate positive correlations for the observer rating scale in both sets, and a minimal involvement for the self rating scale, again in both sets. Each of these canonical correlations are orthogonal, but given the nature of the two domains it is difficult to determine what features are represented in each of the correlations. What does appear is a consistency with

ratings on the Steiner scales.

ii Multiple Correlations

Within Sets

The squared multiple correlations for each variable in the first set with all other variables in the first set, has been presented and discussed in study 1. In summary, there was a strong relationship between the two Steiner scales and the total score, with low multiple correlations for the two VAS.

The multiple correlations for variables in the second set (table 7-13) suggest a moderate interrelationship between these measures at second interview.

Table 7-13

Squared Multiple Correlations for each variable in the second set with all others in the second set

variable	R2
SRS(2)	0.313
ORS(2)	0.405
VAS1(2)	0.257
VAS6(2)	0.161

Between Sets

The multiple correlations for each variable in the first set with all variables in the second set, were consistent with the results of the canonical correlation analysis. Three of the four multiple correlations are significant (table 7-14).

Table 7-14

Squared multiple correlations for each variable in the first set with all variables in the second set

variable	R2	F	df		P
SRS(1)	0.600	13.85	4	37	0.001
ORS(1)	0.501	9.28	4	37	0.001
VAS1(1)	0.152	1.66	4	37	0.180
VAS6(1)	0.254	3.14	4	37	0.025

The multiple correlations for variables in the second set with all variables in the first set, are also consistent with the information given in the two significant canonical correlations (table 7-15).

Table 7-15

Squared Multiple correlations for each variable in the second set with all variables in the first set

variable	R2	F	df		P
SRS (2)	0.423	6.78	4	37	0.001
ORS (2)	0.539	10.80	4	37	0.001
VAS1(2)	0.301	3.98	4	37	0.009
VAS6(2)	0.249	3.07	4	37	0.028

iii. Redundancy Index

The first canonical correlation has a redundancy index of 0.30 for the first set, and 0.30 for the second set. The second canonical correlation has redundancy indices of 0.03 and 0.03, for the first and second set respectively. The overlap between the two sets of variables accounts for only a moderate proportion of the variation within each set.

iv. Summary

These results suggest the two sets of interview data are strongly related. The first two canonical correlations

account for a substantial proportion of the overlap variance (85.5%), and the redundancy index for this suggests the degree of overlap is moderate (33% for both sets). The squared multiple correlations within and between sets, are consistent with the canonical correlations.

7-3-4-2 Interview two and control cycles

The aim of this analysis was to examine the relationship between the second interview's retrospective ratings, and the prospectively collected symptom data, collected for the previous three months. The first set of variables were SRS(2), ORS(2), VAS1(2), VAS6(2). The second set comprised the mood and physical difference scores for the three control cycles.

i Canonical Correlations

The two sets overlap significantly (table 7-16), with the first pair of canonical variates accounting for 54.7% of the overlap variance.

Table 7-16

EIGENVALUE	CANONICAL CORRELATION	NUMBER OF EIGENVALUES	BARTLETT'S TEST FOR REMAINING EIGENVALUES		
			CHI-SQUARE	DF	PROB
			44.84	24	0.006
0.54652	0.73927	1	16.77	15	0.333
0.36856	0.60709	2	0.45	8	0.999
0.01224	0.11064	3	0.01	3	0.999
0.00025	0.01574				

The canonical variable loadings (table 7-17) for the first set were described primarily by VAS1(2), and to a lesser degree by SRS(2) and VAS6(2). The canonical variable

loadings for the second set were strongest for mood and physical symptoms in cycle 2 (as was found in study 1), but in contrast the correlations for the symptom ratings for cycles 1 and 3 were greater.

Table 7-17

	Canonical variable loadings
SET 1	
Canonical Correlation	1
SRS(2)	0.316
ORS(2)	0.681
VAS1(2)	0.903
VAS6(2)	0.624
SET 2	
Canonical Correlation	1
mood symptoms, cycle 1	0.547
physical symptoms, cycle 1	0.449
mood symptoms, cycle 2	0.905
physical symptoms, cycle 2	0.719
mood symptoms, cycle 3	0.585
physical symptoms, cycle 3	0.389

ii Multiple Correlations Between Sets

The multiple correlations between variables within the first set and all variables in the second set (table 7-18) are consistent with the results of the canonical correlation analysis. VAS1(2) is the strongest component of the canonical correlation, followed by the ORS(2). While loading moderately on the canonical correlation, VAS6(2) fails to achieve significance, and SRS(2) was unrelated.

Table 7-18

Squared Multiple correlations for each variable in the first set with all variables in the second set

variable	R2	F	df		P
SRS(2)	0.065	0.41	6	35	0.801
ORS(2)	0.401	3.91	6	35	0.010
VAS1(2)	0.467	5.11	6	35	0.002
VAS6(2)	0.242	1.87	6	35	0.139

The multiple correlations for second set variables with all variables in the first set (table 7-19) are also consistent with the canonical correlation. It appears that the combined battery of interview scales were able to retrospectively predict 3 out of the 6 symptom scores, with the amount of variance accounted for ranging from 27.4% to 46.4%.

Table 7-19

Squared Multiple correlations for each variable in the second set with all variables in the first set

variable	R2	F	df		P
mood (cycle 1)	0.173	1.94	4	37	0.124
physical symptoms (cycle 1)	0.274	3.49	4	37	0.016
mood (cycle 2)	0.464	8.00	4	37	0.001
physical symptoms (cycle 2)	0.284	3.68	4	37	0.012
mood (cycle 3)	0.188	2.13	4	37	0.096
physical symptoms (cycle 3)	0.086	0.87	4	37	0.491

iii Redundancy Index

The redundancy index is 0.24 for the first set, and 0.21 for the second set. The overlap between the two sets of variables therefore accounts for only a moderate proportion of the variation within each set.

iv Summary

These results suggest; (1) the first canonical correlation accounted for a moderate proportion of the overlap variance (54.6%), (2) the redundancy index suggests the amount of overlap was not great.

7-3-4-3 Second and Third Interview

These two sets of interview scores were examined with the expectation of no relationship. The treatment effect should be reflected if retrospective ratings are sensitive to actual events.

i Canonical Correlation

The two sets of variables are independent (table 7-20).

Table 7-20

EIGENVALUE	CANONICAL CORRELATION	NUMBER OF EIGENVALUES	BARTLETT'S TEST FOR REMAINING EIGENVALUES		
			CHI-SQUARE	DF	PROB
			22.91	16	0.1162
0.42881	0.65483	1	9.19	9	0.4204
0.22787	0.47736	2	2.85	4	0.5830
0.09188	0.30312	3	0.49	1	0.4840
0.01980	0.14070				

ii Multiple Correlations

Within Sets

The multiple correlations for interview three (table 7-21) show a similar pattern to interview one and two. The two Steiner scales have the highest correlations with total score, VAS1(3) next highest, and VAS6(3) a relatively low value.

Table 7-21

Squared Multiple Correlations for each variable in the second set with all others in the second set

variable	R2
SRS(3)	0.653
ORS(3)	0.674
VAS1(3)	0.393
VAS6(3)	0.201

Between Sets

Both of the multiple correlation analyses for between sets show no significant relationships, and are consistent with the canonical analysis (tables 7-22, & 7-23).

Table 7-22

Squared Multiple correlations for each variable in the first set with all variables in the second set

variable	R2	F	df	P
SRS(2)	0.157	1.17	4 25	0.3489
ORS(2)	0.201	1.57	4 25	0.2125
VAS1(2)	0.240	1.97	4 25	0.1294
VAS6(2)	0.194	1.51	4 25	0.2309

Table 7-23

Squared Multiple correlations for each variable in the second set with all variables in the first set.

variable	R2	F	df	P
SRS(3)	0.166	1.24	4 25	0.3187
ORS(3)	0.295	2.62	4 25	0.0589
VAS1(3)	0.031	0.20	4 25	0.9375
VAS6(3)	0.256	2.15	4 25	0.1037

iii Redundancy Index

Given the lack of significant overlap between these sets of variables this index is of little interest. For the first

canonical correlation the index is 0.08 and 0.12 for the first and second sets.

v Summary

There is little relationship between scores at second and third interview. This is the expected result given the already described significant treatment effect for the group as a whole.

7-3-4-4 Interview Three and Placebo Cycles

The third interview data were used in this analysis to examine the relationship between such data and prospectively collected symptom records. It is a replication of analysis 2, where the second interview data were related to the control cycles.

i Canonical Correlations

The two sets do not overlap significantly (table 7-24).

Table 7-24

EIGENVALUE	CANONICAL CORRELATION	NUMBER OF EIGENVALUES	BARTLETT'S TEST FOR REMAINING EIGENVALUES		
			CHI-SQUARE	DF	PROB
			31.37	24	0.1435
0.54380	0.73743	1	12.92	15	0.6083
0.33221	0.57638	2	3.43	8	0.9043
0.10417	0.32275	3	0.85	3	0.8379
0.03546	0.18830				

ii Multiple Correlations

Within Sets

The multiple correlations within the second set (table 7-25), suggest there is moderate relationship between the various symptom measures taken over time, most particularly with physical symptoms in cycles 4 and 5. The degree of interrelationship is less than for control cycles, possibly

because of a differential placebo response.

Table 7-25

Squared Multiple Correlations for each variable in the second set with all others in the second set

variable	R2
mood symptoms (cycle 4)	0.198
physical symptoms (cycle 4)	0.539
mood symptoms (cycle 5)	0.334
physical symptoms (cycle 5)	0.613
mood symptoms (cycle 6)	0.215
physical symptoms (cycle 6)	0.398

Between Sets

The multiple correlations between first set variables and second set total score (table 7-26) are consistent with the the canonical correlations with the exception of VAS1(3), which shows a significant multiple correlation with the second set, and accounts for 32.7% of such variance.

Table 7-26

Squared Multiple correlations for each variable in the first set with all variables in the second set

variable	R2	F	df	P
SRS(3)	0.258	1.33	6 23	0.2871
ORS(3)	0.181	0.85	6 23	0.5093
VAS1(3)	0.478	3.51	6 23	0.0224
VAS6(3)	0.327	1.86	6 23	0.1516

The multiple correlations for each variable in the second set and first set total score are consistent with the canonical analysis. None were significant (table 7-27).

Table 7-27

Squared Multiple correlations for each variable in the second set with all variables in the first set.

variable	R2	F	df		P
mood (cycle 4)	0.171	1.29	4	25	0.3021
physical symptoms (cycle 4)	0.075	0.51	4	25	0.7309
mood (cycle 5)	0.048	0.32	4	25	0.8640
physical symptoms (cycle 5)	0.154	1.13	4	25	0.3635
mood (cycle 6)	0.299	2.67	4	25	0.0558
physical symptoms (cycle 6)	0.133	0.96	4	25	0.4465

iii Redundancy Index

The redundancy index is 0.17 for the first set and 0.06 for the second set. The overlap between the two sets of variables is a minor proportion of the variation within each set.

iv Summary

There is little relationship between the scores at interview three and placebo cycle symptom scores. Only VAS1(3) showed any significant multiple correlation with the combined symptom scores. There is less symptom consistency between cycles compared with the scores from control cycles.

7-3-4-5 PMS Distress and Placebo Symptom Scores

The third interview visual analogue scale ratings of Premenstrual Distress for the three placebo cycles (PD1, PD2, PD3 respectively), were the first set of variables in this analysis. The second set were the prospectively collected symptom scores for these cycles (cycle 4 to cycle 6).

i Canonical Correlation

The two sets overlap significantly (table 7-28). The first pair of canonical variates accounts for 51.4% of the

overlap variance.

Table 7-28

EIGENVALUE	CANONICAL CORRELATION	NUMBER OF EIGENVALUES	BARTLETT'S TEST FOR REMAINING EIGENVALUES		
			CHI-SQUARE	DF	PROB
			29.99	18	0.0375
0.51377	0.71678	1	12.69	10	0.2416
0.26990	0.51952	2	5.14	4	0.2733
0.19276	0.43905				

The canonical variable loadings (table 7-29) for the first set were described primarily by the ratings of distress for cycle 5. The canonical variable loadings for the second set were best described by a negative correlation with physical symptoms in cycle 5.

Table 7-29

	Canonical variable loadings
SET 1	
Canonical Correlation	1
PD1	0.027
PD2	0.990
PD3	0.115
SET 2	
Canonical Correlation	1
mood symptoms, cycle 4	0.383
physical symptoms, cycle 4	-0.024
mood symptoms, cycle 5	-0.088
physical symptoms, cycle 5	-0.720
mood symptoms, cycle 6	0.200
physical symptoms, cycle 6	-0.314

ii Multiple Correlations

Within Sets

The multiple correlations within the first set suggest there is almost no relationship between retrospectively rated distress in these cycles (table 7-30).

Table 7-30

Squared Multiple Correlations for each variable in the first set with all other variables in the first set.

variable	R2
PD1	0.023
PD2	0.023
PD3	0.002

Between Sets

The multiple correlations between first set variables and total second set score (table 7-31) are consistent with the canonical correlation in that PD2 (cycle 5) features significantly.

Table 7-31

Squared multiple correlations for each variable in the first set with all variables in the second set

variable	R2	F	df	P
PD1	0.231	1.15	6 23	0.3500
PD2	0.509	3.97	6 23	0.0204
PD3	0.238	1.20	6 23	0.3323

The multiple correlations between each second set variable and all variables in the first set (table 7-32) are also consistent with the canonical correlation. The combined ratings of PMS distress at best predicts 29.7% of the variance of only one of the symptom measures (physical symptom scores, cycle 5).

Table 7-32

Squared multiple correlations for each variable in the second set with all variables in the first set.

variable	R2	F	df		P
mood (cycle 4)	0.199	2.15	3	26	0.1180
physical symptoms (cycle 4)	0.035	0.31	3	26	0.8147
mood (cycle 5)	0.133	1.33	3	26	0.2872
physical symptoms (cycle 5)	0.297	3.67	3	26	0.0250
mood (cycle 6)	0.197	2.13	3	26	0.1210
physical symptoms (cycle 6)	0.123	1.22	3	26	0.3240

iii Redundancy Index

The redundancy index suggests that the overlap is a minor proportion of the variance within each set (0.17 for the first set, and 0.07 for the second set).

iv Summary

The first canonical correlation accounts for a significant proportion of the overlap variance (51.4%), but the redundancy indices suggest the degree of overlap is small (0.17 and 0.07 respectively for set one and set two). Consistency within sets is low. The one significant canonical correlation links a narrow band of the total domains.

7-3-4-6 Ratings of Treatment Effectiveness and Placebo Cycles

The visual analogue scale ratings of treatment effectiveness for the three placebo cycles (TE1, TE2, TE3 repectively) were the first domain. The second domain was the mood and physical symptom scores for those cycles.

i Canonical Correlation

The two sets do not show significant overlap (table 7-33).

Table 7-33

EIGENVALUE	CANONICAL CORRELATION	NUMBER OF EIGENVALUES	BARTLETT'S TEST FOR REMAINING EIGENVALUES		
			CHI-SQUARE	DF	PROB
			26.18	18	0.0957
0.53725	0.73298	1	7.69	10	0.6595
0.24654	0.49653	2	0.89	4	0.9257
0.03648	0.19100				

ii Multiple Correlations

Within Sets

As with PMS distress, the multiple correlations for treatment effectiveness ratings show little consistency across cycles (table 7-34).

Table 7-34

Squared multiple correlations for each variable in the first set with all other variables in the first set.

variable	R2
TE1	0.113
TE2	0.130
TE3	0.201

Between Sets

The multiple correlations between first set variables and total score for the second set are consistent with the canonical correlation. None of the variables is significant (table 7-35). Only the rating of treatment effectiveness for cycle 5 approaches significance. This is the same cycle represented in the canonical correlation in the previous analysis.

Table 7-35

Squared Multiple correlations for each variable in the first set with all variables in the second set

variable	R2	F	df	P
TE1	0.053	0.21	6 23	0.8863
TE2	0.436	2.97	6 23	0.0532
TE3	0.306	1.69	6 23	0.1970

The multiple correlations for each second set variable with all first set variables are also consistent with the canonical analysis, with the exception of cycle 6 mood, which is significant (table 7-36). Treatment effectiveness ratings do predict, but only one cycle's mood symptoms.

Table 7-36

Squared multiple correlations for each variable in the second set with all variables in the first set.

variable	R2	F	df	P
mood (cycle 4)	0.061	0.56	3 26	0.6447
physical symptoms (cycle 4)	0.108	1.05	3 26	0.3884
mood (cycle 5)	0.149	1.52	3 26	0.2330
physical symptoms (cycle 5)	0.075	0.71	3 26	0.5561
mood (cycle 6)	0.307	3.85	3 26	0.0210
physical symptoms (cycle 6)	0.032	0.29	3 26	0.8357

iii Redundancy Index

The redundancy index is 0.19 for the first set and 0.08 for the second set. The overlap between the two sets of variables accounts for a minor proportion of the variation within each set.

iv Summary

There is no significant overlap between the domains of treatment effectiveness ratings and prospectively rated

symptoms. There is some predictive power within the first set of variables but only for cycle 6 mood. These ratings are therefore of limited value.

7-3-4-7 Treatment Effectiveness and PMS Distress Ratings With Placebo Cycles

The third interview VAS ratings of treatment effectiveness overall (TEOA) and premenstrual distress overall (PDOA) were the first set in this analysis. The second set comprised:- (1) mean mood difference score for placebo cycles (psyc4-6), (2) mean physical symptom difference score for placebo cycles (phys4-6), (3) mean standardized symptom score for placebo cycles (symp4-6).

i Canonical Correlation

The two sets do not show significant overlap(table 7-37).

Table 7-37

EIGENVALUE	CANONICAL CORRELATION	NUMBER OF EIGENVALUES	BARTLETT'S TEST FOR REMAINING EIGENVALUES		
			CHI-SQUARE	DF	PROB
			10.96	6	0.0896
0.21852	0.46746	1	4.55	2	0.1027
0.16058	0.40072				

ii Multiple Correlation

Within Sets

The multiple correlations for variables within the first set suggest little relationship exists between treatment effectiveness ratings and ratings of PM distress (table 7-38).

Table 7-38

Squared Multiple Correlations for each variable in the first set with all other variables in the first set.

variable	R2
TEOA	0.131
PDOA	0.131

The multiple correlations for the variables within the second set suggest there is a strong relationship between the symptom measures (table 7-39). This strength of relationship is difficult to interpret as the standardised symptom scores (symp4-6) were a simple transformation of the mood and physical symptom scores. Including the standardised scores inflates the relationship between each of the variables and total score. Their major value is their function as the criterion.

Table 7-39

Squared Multiple Correlations for each variable in the second set with all others in the second set

variable	R2
psyc4-6	0.812
phys4-6	0.928
symp4-6	0.957

Between Sets

The multiple correlations for variables in the first set, with second set total scores (table 7-40), are consistent with the canonical correlations. No overlap or predictability exists.

Table 7-40

Squared Multiple correlations for each variable in the first set with all variables in the second set

variable	R2	F	df	P
TEOA	0.218	2.42	3 26	0.1084
PDOA	0.169	1.76	3 26	0.1917

The multiple correlations for each second set variable with first set total scores (table 7-41) also reflects the canonical correlation, with no relationships evident.

Table 7-41

Squared Multiple correlations for each variable in the second set with all variables in the first set.

variable	R2	F	df	P
psyc4-6	0.011	0.16	2 27	0.8565
phys4-6	0.160	2.57	2 27	0.0949
symp4-6	0.119	1.82	2 27	0.1813

iii Redundancy Index

The redundancy index for the first canonical correlation was 0.13 and 0.01 for the first and second set respectively. For the second canonical correlation the index was 0.07 and 0.09 for the first and second set respectively.

iv Summary

No relationship exists between retrospective ratings of both distress and treatment effectiveness and concurrent symptom scores.

7-4 Discussion

7-4-1 Method

Methodological difficulties are plentiful in the study of PMS. The study reported in this chapter has taken the same steps as were taken in study 1 to minimize these difficulties. These include minimal intrusion into the lives

of the subjects, inclusion criteria which required the absence of all but trivial health problems and life stressors, and the measurement of relative change in severity of symptoms rather than absolute level. The continued low rate of annovulatory cycles avoids rather than confronts the controversy about the presence of PMS in such cycles.

The design chosen was a variation of the traditional cross-over design where, rather than following the baseline period with both drug and placebo in random first position, 19 women received placebo only. Some (11) continued recording for an additional month. This design was chosen for a number of reasons. Firstly, after 3 cycles of recording there was resistance to continued recording for another 3 cycles. Secondly, the strong possibility of asymmetrical transfer effects (Millar 1983) makes the traditional cross-over design only useful if one carefully examines order effects. Thirdly, considerable between-subject variablility increases the risks involved with reducing the number of subjects. As a consequence the lack of order effects found within control and placebo cycles was crucial. The fourth cycle of control recording for the 11 subjects did not result in a significant difference between these subjects and those who had begun placebo treatment. There were however, nonsignificant trends in the expected direction. The lack of significant differences between cycles 3 and 4 for the control group suggests the additional month of recording does not have a significant effect. The most obvious problem was considerable variablity shown by subjects, which when combined with reduced numbers of subjects, reduced the size of any effects. This affects both the comparisons between cycles 3 and 4, and within cycle 4 between the control and placebo groups.

Consequently, the credibility of the design and interpretation is dependent upon the lack of order effects within the total group.

7-4-2 Results

7-4-2-1 Incidence

For each symptom type incidence decreased significantly under placebo compared with baseline recording. The lack of significant variation attributable to group and symptom type parallels the results in study 1, and suffers the same interpretive problems since groups were constituted on the basis of symptom severity. The significant group*mode interaction differs from study 1. The decreasing trend across severity groups for psychological symptoms raises the possibility that treatment, when examined at group*mode level, differentially affected symptom type. This effect may have been lost in the examination of groups and mode because they were respectively collapsed across treatment and mode, and treatment and groups.

Incidence is often calculated independent of which symptom type is present in the cycle. Defined this way, incidence showed no group or treatment effects. These results are similar to study 1 and again indicate that retrospective self-rating of severity is a poor indicator of incidence or consistency of symptom expression over months. Mean incidence is again less than every cycle.

7-4-2-2 Severity

The lack of variation across cycles (order effect) is similar to study 1. This applies to both approaches used to quantify severity. As previously noted, lack of order effects was critical to interpretation of treatment effects. Had order effects been present (particularly a downward trend

over cycles) a spurious treatment effect could have resulted.

Difference scores for both psychological and physical symptoms showed a decline in severity under the treatment condition. Results for the other independent variables parallel study 1, with mood severity varying significantly and consistently with groups. It was unclear whether the treatment effect and the group effect for mood scores was the result of mid-cycle or premenstrual change. This was examined with phase scores.

The phase score analysis shows mood to be higher during placebo than control cycles and to be lower premenstrually compared to mid-cycle. The absence of the significant variation in mood severity across groups is likely to be the result of collapsing across phase. The significant interaction between groups and phases supports this, and as with study 1 suggests that the source of variation is within the premenstrual rather than mid-cycle scores. A similar situation exists with treatment. The significant interaction between treatment and phase, together with mean scores, suggests treatment has its effects upon premenstrual scores rather than at midcycle. This also applies to physical symptom scores where there was no significant variation across groups, mean scores were lower (less severe) under placebo and the effect was specific to the premenstrual phase.

7-4-2-3 Interview Results

Interviews one and two overlap to the extent of about 30% of the total variance. Within this overlap they are quite strongly related but it is not clear which of the interview components contribute to this beyond the consistent

appearance of the two Steiner scales. Given that this was a retest three months later, the lack of overlap is disappointing, but consistent with other studies (eg., Harrison et al., 1984; Endicott & Halbreich, 1982).

When compared with those symptoms in the cycles supposedly reflected in the ratings, interview 2 conclusions were similar to those of study 1. The VAS rating severity over the previous month was the most powerful predictor of overall symptom scores and showed a linkage to the symptoms in cycle 2. There was an increase in the amount of overlap and the degree to which this overlap is accounted for. To this extent the prospective recording may have improved the subjects' ability to comply.

The comparison between the second and third interviews suggests they were independent or non-overlapping. This was as expected given the significant treatment effect.

The comparison between interview three and placebo cycle symptoms suggested no significant overlap, although again VAS1 was the best predictor.

The ratings of Premenstrual distress for placebo cycles compared with symptom ratings for those months, show minor but significant overlap. Most of the linkage between these domains is negative and between distress ratings and symptoms on cycle 5.

The ratings of treatment effectiveness show no significant overlap with the symptom ratings over the corresponding period of time.

The ratings of both overall treatment effectiveness and overall distress also show no significant overlap with the symptom ratings over the corresponding period of time.

CHAPTER EIGHT - SPECTRAL ANALYSIS

8-1 INTRODUCTION

The purpose of this study was to explore the use of spectral analysis as a means of overcoming methodological problems associated with cyclicity in the diagnosis of PMS. The aims were as detailed below.

1. To directly establish the presence or absence of cyclicity at the period equivalent to the menstrual cycle. Previous studies have established cyclicity by a variety of techniques, each varying in the degree of adequacy. Inadequate studies do not provide supporting evidence for the existence of cyclicity (eg., Backstrom & Mattsson, 1975), and measure symptoms during one fixed period in the cycle (eg., Graham, Harding, Wise, & Berriman, 1978).

The use of the difference between follicular and premenstrual scores (O'Brien et al) is more acceptable. However interpretation is limited in that mid-cycle (follicular) variablity cannot be separated from premenstrual variation (chapter 6; Sampson and Prescott, 1981). A recent alternative procedure uses cycle phase as an independent variable and the presence of a phase main effect as evidence of cyclicity. The disadvantages of these approaches are the need to analyse group data (Parlee, 1973; Kruse & Gottman, 1982), and the impact of autocorrelation on levels of significance (Gottman, 1981).

The most sophisticated alternative uses a fitted sine wave to describe prospectively collected data (Sampson & Jenner, 1977). This approach does not avoid all the difficulties. The assumption of deterministic rather than

stochastic variation is not a serious threat when examining one cycle. However serious reduction in goodness of fit is likely if more than one cycle is used. This is a problem if symptom expression is not expected to be constant over cycles, and several cycles are therefore collected to provide a stable baseline. Other unused techniques, such as fitting polynomials, involve similar problems. A further problem is, if one assumes deterministic cycles and constancy of expression, one must also ignore the possibility of non-menstrual stressors generating symptoms during the premenstrual phase.

Spectral analysis (see Chapter 5) overcomes these problems and provides a method of directly assessing significant cyclicity.

2. To provide another way of examining the issues of retrospective diagnosis and modifying negative expectations (chapters 6 & 7). A direct comparison of ANOVA and spectral analysis approaches is of interest for two reasons. Firstly, analysis at the individual level prevents the loss of theoretical and practical significance induced by averaging across heterogenous subjects (Parlee, 1973; Kruse & Gottman, 1982). Some empirical support exists for the advantages of time series analysis over analysis of variance (Ward et al., 1983; Dahlstrom, 1983)

3. To use Spectral analysis to investigate the existence of other cycles such as weekly, and the relationship between symptom types. Of particular interest was the distinction between psychological and physical symptoms. These two categories of symptoms are frequently treated differently. Some authors emphasise psychological symptoms (Wetzel et al, 1975; Haskett et al, 1984), others emphasise physical

symptoms such as oedema and weight gain (Janowsky et al., 1973) This dichotomy is also illustrated in Steiner et al's (1980) approach where physical symptoms are included in the rating scales but not in the Research Diagnostic Criteria.

Spectral analysis will be used as an exploratory method, where there are few grounds for a priori models (Jenkins & Watts, 1968).

8-2 METHOD

8-2-1 Introduction

The data generated for study 2 were used in the analyses presented in this chapter. The subjects, procedure and instruments were the same as described in chapter 7.

8-2-2 Analysis.

For control and placebo cycles each subject's daily mood and physical symptom scores were analysed using BMDP1T (Dixon, 1981). Files were visually examined in order to reject cycles with more than 5 days missing from the premenstruum, and then missing values were replaced using the programme's default linear interpolation method. This was rare as most subjects either ceased recording or missed at most two or three points per cycle. Data preceeding the beginning of the first menstrual period were removed, as were any data from the incomplete cycles at the end of the study. Default bandwidths at 8, $3n^{1/3}$, and $n^{2/3}$ degrees of freedom (n being the number of observations) were accepted, but generally $3n^{1/3}$ was interpreted as a compromise between resolution and stability. Log transformations of spectral density were plotted, as this results in equal length confidence intervals for all frequencies (Dixon, 1981). The significance of peaks in log spectral density were assessed using the technique described in Kruse and Gottman (1982) and

Koopmans (1974). In the bivariate analyses of mood and physical symptoms, the confidence intervals for coherence were calculated by the method suggested by Jenkins and Watts (1968). A critical level was established to ensure there was no overlap between the 95% confidence intervals around it and a coherence of zero. Coherence was interpreted provided it exceeded this critical level and there were significant peaks in the respective spectral density functions. Phase and slope of the phase plot were interpreted, provided coherence exceeded the critical level and there were significant peaks within both of the spectral density functions (Gottman, 1979; 1981).

8-3 RESULTS

8-3-1 Overview

Spectral density analysis results will be presented in detail for one subject (S4) as an illustration of an individual analysis. The rest of the results will be interpreted and presented according to the aims listed above. The raw data graphs and spectral density material for remaining subjects are presented in appendix 5 and 6.

The actual menstrual cycle lengths, with means and standard deviations, are presented in table 8-1. The range of these values was between 23.3 and 34.6 days. Therefore, in interpreting the spectral density, peaks occurring within this range were accepted as being menstrual cycle congruent.

Table 8-1

Menstrual Cycle Length
(days)

subject	c1	c2	c3	c4	c5	c6	c7	c8	mean cont c.	s d cont c.	mean plac c.	s d plac c.
01	24	22	25	26	23	23			23.7	1.57	24.0	1.73
02	27	26	25	28	24	26	26		26.0	1.00	26.0	1.63
04	25	24	22	26	23	26	24	25	24.3	1.71	24.5	1.29
05	31	27	29	27	31	27	28		28.5	1.92	28.7	2.08
07	33	25	27	25	30	27			28.3	4.16	27.3	2.52
08	26	25	26	27	27	25	27		25.7	0.58	26.5	2.00
10	27	29	28	29	24	29			28.3	0.96	28.0	2.00
11	19	26	28	27	24	29			24.3	4.73	26.7	2.52
14	25	23	24	23	24	25	25		23.8	0.96	24.7	0.58
15	26	26	27	27	27	28			26.3	0.58	27.3	0.58
16	23	25	22	26	24	28			23.3	1.53	26.0	2.00
17	30	30	33	32	44	28			31.0	2.08	34.6	8.33
18	28	31	32	26	34	26			30.3	2.08	28.7	4.62
20	28	25	27	24	26	32			26.7	1.53	27.3	4.16
21	24	23	24	24	23	23	23		23.8	0.50	23.0	0.00
25	23	26	25	23	23	25	24		24.3	1.50	24.0	1.00
29	24	23	25	25	26	25			24.0	1.00	25.3	0.58
30	26	25	23	24	24	24	24		24.5	1.29	24.0	0.00
32	26	24	22	24	28	23			24.0	2.00	25.0	2.65
35	28	25	30	32	28	29	31		27.7	2.52	30.0	1.83
36	27	26	25	23	30	19			26.0	1.00	24.0	5.57
37	31	31	30	31	31	31	31		30.8	0.50	31.0	0.00
38	22	22	24	22	24	24			22.7	1.16	22.7	1.16
39	31	26	28	26	27	28			28.3	2.52	27.0	1.00
44	24	26	26	25	28	24			25.3	1.16	25.7	2.08
45	27	25	26	26	25	25	26		26.0	0.82	25.3	0.58
46	29	24	24	23	24	26	25		25.0	2.71	25.0	1.00
48	27	25	26	30	26	27	24		27.0	2.16	25.7	1.53
49	28	33	28	28	25	26			29.7	2.89	26.3	1.53
50	25	24	24	25	25	26			24.3	0.58	25.3	0.58

c1 = cycle one, c2 = cycle two etc.

cont c. = control cycles. plac c. = placebo cycles.

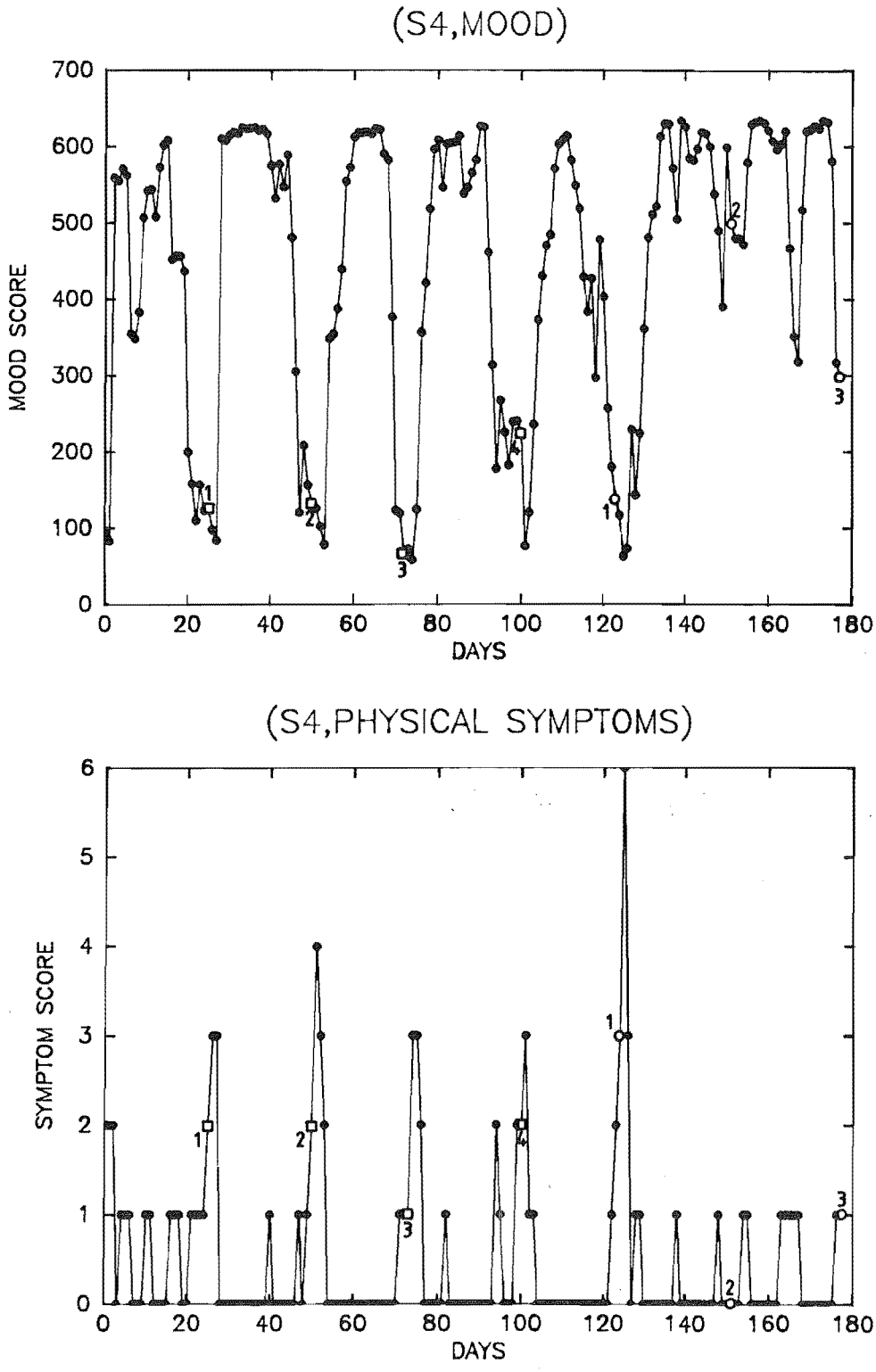
8-3-2 A single subject analysis

Daily mood scores (fig. 8-1) showed a decrease in mood or feelings of well being, around the onset of menstruation in most of the seven cycles. The exception was cycle 2 under placebo where the decrease was minimal and not clearly discriminable from mood scores reported for the rest of the cycle. It was also apparent that the mood disturbance continued or became more pronounced during the first one to three days of bleeding eg., the fourth control cycle (fig. 8-1). A similar situation existed for physical symptoms with clear increases around the onset of menstruation and continuing for one to three days, with the exception of the second placebo cycle.

The mood and physical symptom spectral densities for control cycles showed the same broad outlines (fig. 8-2). The significant peaks in both series were broad (9.3 to 102 days for mood and 14.5 to 102 days for physical symptoms (table 8-2) but peak at 26 days. This was within the range of menstrual values and was congruent with S4's mean (sd) of 24.3 (1.71) days actual menstrual cycle length. The coherence between mood and physical symptoms (table 8-3) was significant over the range of 14.5 to 102 days with a peak at 26 days. This fits with the significant peaks for both series in each of the spectral density functions.

Figure 8-1

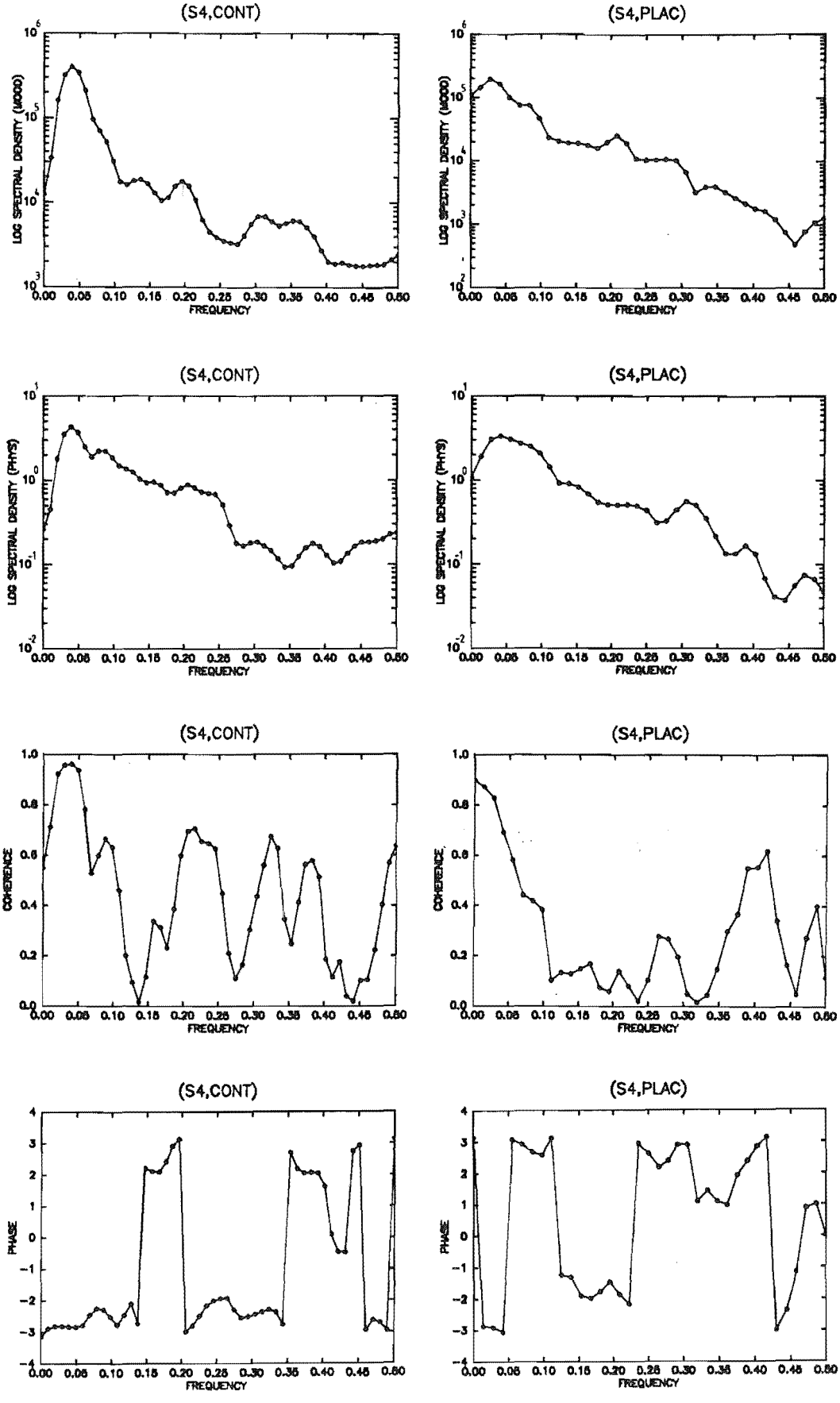
Mood and Physical Symptoms for Control and Placebo Cycles



□ = Control cycle 1 (etc)

○ = Placebo cycle 1 (etc)

Figure 8-2
Spectral Density, Coherence, and Phase for Control and Placebo Cycles



For control cycles the phase at the peak frequency (f=0.0392) was -2.825 which suggests there was a 12 day delay at this frequency. This approximates half the cycle and was a consequence of the opposite directions in which increased severity was reflected for mood and physical symptoms. The slope of the phase plot over the range of significant coherence (table 8-3) was -0.2 which suggests that the input series (mood) leads but only by 0.03 days.

For placebo cycles the spectral density functions showed similar but less well defined peaks in both the mood and physical symptom series (fig. 8-2). The range of significant cyclicity for mood (24 to 72 days) overlaped with menstrual values but the peak was displaced towards a longer period (36 days)(table 8-2). This was probably a result of fewer data points (72 in placebo as opposed to 101 in control cycles) and therefore of no significance. The range of significant cyclicity for physical symptoms (9 to 72 days) (table 8-2) peaked at 24 days which was congruent with menstrual cycle values and the actual mean (sd) menstrual cycle length of 24.5 (1.29) (table 8-1). The coherence between mood and physical symptoms was significant over the range of 23.9 to 72 days (table 8-3). This fits with the significant peaks in the spectral density functions for each series. The phase at the peak frequency (f=0.0278) was -2.980 and correspond to an aproximately 17 day delay. Again this was a consequence of the opposite directions in which an increase in symptom severity was scored. The slope of the phase over the range of significant coherence was -3.6 which suggests mood leads by approximately 0.6 days.

TABLE 8-2

NUMBER OF DATA POINTS (T), BANDWIDTH (BW), MEAN SPECTRAL DENSITY AND SIGNIFICANT CYCLICITY WITHIN SPECTRAL DENSITY ESTIMATES BY SUBJECT (S), TYPE OF CYCLE (C=CONTROL, P=PLACEBO), AND TYPE OF SYMPTOM (M=MOOD, P=PHYSICAL)

S	CYCLE/ SYMPT	T	BW	MEAN SP DENSITY	SUM OF PEAK	PERIOD RANGE PEAK	PEAK CENTRE	CHI SQ	DF	SIG
1	C/M	74	.0897	5689.9	139350	9.7- 78	25.9	343	112	.005
	C/P	"	"	1.68	47.60	6.5- 78	25.9	396	168	.005
	P/M	"	"	3268.8	28626	2.1- 2.5	2.4	123	98	.05
	P/P	"	"	1.25	27.34	12 - 72	24	284	70	.005
2	C/M	80	.0824	14666	382879	12 - 85	42.5	365	98	.005
	C/P	"	"	1.15	31.86	17 - 85	28	355	65	.005
	P/M	108	.0673	19474.5	804040	17 -104	25.9	578	98	.005
	P/P	"	"	1.49	48.17	8 -104	25.9	452	168	.005
4	C/M	101	.0686	38925	1736250	9.3-102	26	624	154	.005
	C/P	"	"	0.84	15.89	14.5-102	26	265	70	.005
	P/M	72	.0694	31692.	501000.	24 - 72	36	158	30	.005
	P/P	"	"	0.84	20.05	9.0- 72	24	238	80	.005
5	C/M	123	.0560	7873.	356811.	8.3-125	31.3	634	210	.005
	C/P	"	"	0.44	8.13	11.4- 63	31.3	258	84	.005
	"	"	"	"	2.89	6.0- 6.9	6.4	92	56	.005
	P/M	83	.0833	4845.	55047.	12.0- 84	21.0	159	98	.005
	"	"	"	"	40902.	5.9- 8.4	7.0	118	70	.005
	P/P	"	"	0.46	9.08	9.3- 84	28.0	275	126	.005
7	C/M	93	.0737	8226.	181570.	11.9- 95	31.6	309	98	.005
	C/P	"	"	0.75	15.12	19.0- 95	31.6	281	70	.005
	"	"	"	"	13.50	7.3- 15.8	11.8	251	112	.005
	P/M	80	.0875	6887.	144570.	10.0- 80	26.6	293	112	.005
	P/P	"	"	0.58	17.91	8.8- 80	26.6	429	126	.005

Cont/-

Table 8-2 continued: -

8	C/M	84	.0833	8613.	208072.	12.0- 84	28.0	338	98	.005
	C/P	"	"	2.36	57.73	12.0- 84	28.0	342	98	.005
	P/M	105	.0667	2162.	93259.	8.1-105	26.2	604	182	.005
	P/P	"	"	1.18	56.90	14.9-105	26.2	464	84	.005
10	C/M	121	.0579	9465.	105780.	12.1- 20.2	15.1	156	70	.005
	"	"	"	"	138580.	5.8- 8.1	6.7	205	98	.005
	C/P	"	"	1.35	46.04	17.3-120	30.2	477	98	.005
	"	"	"	"	10.17	8.1- 12.1	8.9	105	70	.005
	P/M	83	.0595	1848.	NO PEAKS					
	P/P	"	"	1.01	12.71	21.0- 42.0	28.0	126	30	.005
	"	"	"	"	12.06	12.0- 16.8	14.0	120	30	.005
11	C/M	81	.0864	23945.	716710.	11.6- 81	27.0	419	98	.005
	C/P	"	"	1.93	41.4	13.5- 81	40.	301	84	.005
	P/M	78	.0897	20355.	686911.	4.6- 78	25.9	472	238	.005
	P/P	"	"	0.52	NO PEAKS					
14	C/M	98	.0714	7513.	216810.	14.0- 98	24.5	404	98	.005
	C/P	"	"	2.28	60.22	16.3- 49	24.5	369	70	.005
	P/M	78	.0897	3829.	81645.	7.1- 39	13.0	299	140	.005
	P/P	"	"	1.23	32.25	11.2- 78	25.9	368	98	.005
15	C/M	87	.0795	24234.	471410.	11.0- 69	29.3	272	112	.005
	C/P	"	"	1.17	15.21	17.6- 69	29.3	181	70	.005
	P/M	80	.0625	25186.	536030.	13.3- 80	40.0	213	60	.005
	P/P	"	"	1.16	22.60	13.3- 80	40.0	194	60	.005
16	C/M	77	.0649	17246.	362905.	6.4- 38	25.6	210	110	.005
	C/P	"	"	0.25	0.84	4.5- 4.8	4.6	34	20	.05
	P/M	77	.0909	7779.	51320.	25.6- 77	38.5	92	42	.005
	"	"	"	"	68875.	7.0- 15.4	12.8	124	84	.005
	P/P	"	"	0.09	0.53	19.3- 77	25.6	80	56	.025
	"	"	"	"	1.03	3.5- 4.8	4.0	155	98	.005
17	C/M	100	.0700	8943.	153009.	14.0-100	25.0	239	98	.005
	C/P	"	"	1.07	23.09	20.0-100	33.3	344	70	.005

Cont/-

Table 8-2 continued: -

	P/M	103	.0481	7865.	113858.	25.9-104	52.1	145	40	.005
	"	"	"	"	63638.	6.5- 9.5	7.4	81	60	.05
	P/P	"	"	0.69	23.23	20.8-104	44.	335	50	.005
18	C/M	101	.0686	960.	21017.	8.5-102	34.	307	168	.005
	"	"	"	"	11916.	4.4- 7.3	6.0	178	140	.025
	C/P	"	"	1.02	44.33	6.0-102	34.	606	238	.005
	P/M	82	.0833	553.	6333.	14.0- 84	28.0	158	84	.005
	"	"	"	"	5360.	4.2- 5.6	4.8	134	84	.005
	P/P	"	"	0.58	NO PEAKS					
20	C/M	87	.0795	6922.	153260.	12.6- 88	29.3	310	98	.005
	"	"	"	"	56514.	6.3- 8.8	8.3	114	70	.005
	C/P	"	"	0.85	12.96	14.6- 88	19.3	214	84	.005
	"	"	"	"	11.33	5.2- 11.0	8.8	187	140	.005
	P/M	81	.0617	4960.	70324.	13.5- 81	20.2	142	60	.005
	P/P	"	"	1.06	25.54	13.5- 81	27.0	240	126	.005
21	C/M	103	.0673	21823.	449030.	17.3- 52	34.7	288	70	.005
	"	"	"	"	162780.	5.8- 7.4	6.5	104	70	.005
	C/P	"	"	1.56	27.20	17.3- 52	25.9	244	70	.005
	"	"	"	"	8.02	9.5- 11.6	10.4	72	42	.005
	"	"	"	"	7.67	6.5- 7.4	6.9	69	42	.005
	P/M	68	.1029	7864.	84614.	13.6- 68	34.7	151	70	.005
	"	"	"	"	64568.	6.2- 9.7	7.6	115	70	.005
	P/P	"	"	0.11	0.60	17.3- 68	34.7	76	56	.05
	"	"	"	"	1.40	4.9- 11.3	6.8	176	126	.005
25	C/M	105	.0667	6792.	137470.	17.5-105	34.9	283	84	.005
	"	"	"	"	38650.	10.5- 13	11.6	80	42	.005
	C/P	"	"	1.55	40.21	15.0- 53	26.3	363	84	.005
	P/M	71	.0972	5109.	108572.	9.0- 72	18.0	297	112	.005
	P/P	"	"	0.49	5.70	9.0- 18	14.4	162	70	.005
29	C/M	78	.0897	5959.	156893.	7.8- 78	25.9	368	140	.005
	C/P	"	"	5.13	162.49	7.8- 78	25.9	444	140	.005

Cont/-

Table 8-2 continued: -

	P/M	76	.0921	4409.	57727.	9.5- 76	15.2	183	112	.005
	"	"	"	"	53639.	4.8- 7.6	6.3	170	98	.005
	P/P	"	"	1.60	32.44	8.5- 76	25.3	284	126	.005
30	C/M	107	.0648	7279.	96090.	9.8- 15.4	13.5	184	70	.005
	C/P	"	"	4.96	183.53	15.4-107	27.0	518	98	.005
	P/M	70	.1000	2486.	24884.	11.7- 70	23.3	140	84	.005
	"	"	"	"	25500.	5.0- 8.8	6.4	144	98	.005
	P/P	"	"	4.07	87.02	11.7- 70	23.3	300	84	.005
32	C/M	78	.0641	8688.	83450.	25.9- 78	39	96	30	.005
	"	"	"	"	123396.	8.7- 15.6	11.4	142	50	.005
	C/P	"	"	1.42	12.95	19.4- 78	25.9	128	30	.005
	"	"	"	"	22.25	7.8- 15.6	13.0	220	60	.005
	P/M	74	.0933	7443.	171000.	10.7- 75	25.0	322	98	.005
	P/P	"	"	1.86	53.19	6.3- 75	18.8	400	168	.005
35	C/M	91	.0769	4647.	115400.	7.0- 91	10.1	348	182	.005
	C/P	"	"	1.48	48.83	7.0- 91	30.3	462	182	.005
	P/M	119	.0588	4113.	55903.	13.0- 60	29.8	190	98	.005
	"	"	"	"	45907.	7.0- 11.9	8.8	156	112	.005
	P/P	"	"	0.98	32.72	11.9- 60	29.8	469	126	.005
36	C/M	85	.0824	17839.	412700.	10.6- 85	21.2	324	112	.005
	"	"	"	"	161460.	5.3- 8.5	7.0	127	98	.05
	C/P	"	"	1.55	36.00	10.6- 85	21.2	334	112	.005
	P/M	71	.0694	13394.	229078.	7.2- 36	23.9	171	126	.005
	P/P	"	"	0.55	10.19	14.4- 72	23.9	185	70	.005
37	C/M	129	.0692	15368.	849214.	10.0-130	32.5	995	234	.005
	C/P	"	"	3.65	207.81	10.0-130	32.5	1026	234	.005
	P/M	93	.0737	13260.	489876.	7.3- 95	23.8	517	182	.005
	P/P	"	"	4.39	182.84	7.3- 95	23.8	584	182	.005
38	C/M	74	.0933	8922.	294453.	5.3- 75	25.0	462	210	.005
	C/P	"	"	2.50	84.97	5.3- 75	25.0	475	210	.005
	P/M	70	.1000	4724.	137120.	3.9- 70	35.0	406	252	.005

Cont/-

Table 8-2 continued: -

	P/P	"	"	1.77	58.36	3.9- 70	17.5	462	252	.005
39	C/M	93	.0737	16974.	216440.	7.9- 15.8	11.8	179	98	.005
	C/P	"	"	2.45	51.76	15.8- 95	47	295	84	.005
	P/M	79	.0875	11038.	NO PEAKS					
	P/P	"	"	1.77	31.46	13.3- 80	26.6	248	84	.005
44	C/M	83	.0833	10666.	61760.	10.5- 14	11.2	81	56	.025
	"	"	"	"	65620.	6.5- 8.4	8.0	86	126	.025
	C/P	"	"	5.61	173.70	9.3- 84	28.0	433	126	.005
	P/M	76	.0921	9310.	137150.	7.6- 15.2	10.8	206	84	.005
	P/P	"	"	0.65	14.95	9.5- 75	25.3	322	112	.005
45	C/M	113	.0614	9593.	445292.	9.5-114	28.5	650	168	.005
	C/P	"	"	1.21	49.52	9.5-114	28.5	571	168	.005
	P/M	74	.0933	9233.	271450.	8.3- 75	25.0	412	126	.005
	P/P	"	"	0.76	13.31	8.3- 75	25.0	247	126	.005
46	C/M	109	.0455	12660.	321534.	12.2-110	36.6	254	90	.005
	C/P	"	"	2.55	90.91	13.8-110	55	356	90	.005
	P/M	73	.0933	13303.	131730.	15.0- 75	37.5	139	70	.005
	"	"	"	"	85210.	8.3- 12.5	10.7	90	56	.005
	P/P	"	"	2.88	76.96	9.4- 75	25.0	374	112	.005
48	C/M	116	.0427	3150.	45694.	29.2-117	58	145	40	.005
	"	"	"	"	20587.	14.6- 23.4	23.4	71	40	.025
	C/P	"	"	0.28	8.72	13.0- 59	19.5	314	80	.005
	P/M	76	.0921	1919.	23464.	8.4- 76	25.3	171	126	.005
	P/P	"	"	0.35	9.34	7.6- 76	25.3	374	140	.005
49	C/M	95	.0737	15009.	386280.	10.6- 95	23.8	360	126	.005
	C/P	"	"	1.52	27.51	9.5- 95	31.6	253	140	.005
	"	"	"	"	15.40	5.0- 7.9	5.9	142	112	.05
	"	"	"	"	13.29	3.7- 4.8	4.1	122	98	.05
	P/M	78	.0897	11215.	275670.	9.8- 78	19.5	344	112	.005
	P/P	"	"	0.33	4.32	6.0- 11.1	7.8	185	140	.025
	"	"	.0641	0.33	4.44	15.6- 78	39	136	50	.005

Cont/-

Table 8-2 continued: -

50	C/M	80	.0875	1118.	11445.	16.0- 80	40	143	70	.005
	C/P	"	"	0.32	2.63	16.0- 80	40	113	70	.005
	"	"	"	"	2.60	4.7- 6.7	5.7	112	84	.025
	P/M	73	.0933	808.	9235.	12.5- 75	25.0	160	84	.005
	P/P	"	"	0.51	9.28	3.9- 15	8.3	253	210	.025

Table 8-3

COHERENCE AND PHASE RELATIONSHIPS WITHIN SPECTRAL DENSITY ESTIMATES BY SUBJECTS, AND TYPE OF CYCLE (C=CONTROL, P=PLACEBO).

S	CYCLE TYPE	PERIOD RANGE OF SIG. COH. (DAYS)	PEAK CENTRE (DAYS)	PHASE AT PEAK (RADS)	DELAY AT PEAK (DAYS)	SLOPE OF PHASE	LEAD INDICATOR/ LEAD (DAYS)
1	CONT	25.9 - 78	39	2.936	18.6	4.8	PHYS/0.8
1	PLAC	7.2	7.2	--	--	--	---
2	CONT	21.2 - 43	28.3	2.700	13	2.8	MOOD/0.5
2	PLAC	17.3 - 35	25.9	2.482	10.2	10.6	MOOD/1.7
4	CONT	14.5 -102	26	-2.825	12	0.2	MOOD/0.03
4	PLAC	23.9 - 72	35.9	-2.980	16.6	3.6	MOOD/0.6
5	CONT	9.6 - 42	31.5	3.073	15		---
5	PLAC	3.4 - 4	3.7	--	--	--	---
7	CONT	19 - 95	31	-2.728	14	5.2	MOOD/0.8
7	PLAC	11.4 - 80	26.6	3.076	13	7.2	MOOD/1.2
8	CONT	16.8 - 84	28.0	2.788	12.5	9.1	PHYS/1.5
8	PLAC	21.0 - 53	34.9	-3.051	16.9	4.6	PHYS/0.8
10	CONT	---	--	--	--	--	---
10	PLAC	---	--	--	--	--	---
11	CONT	20.2 - 81	40.5	-3.050	19.6	5.5	MOOD/0.9
11	PLAC	---	--	--	--	--	---
14	CONT	19.6 - 98	49.0	3.037	23.7	0	---
14	PLAC	---	--	--	--	--	---
15	CONT	29.3 - 44.1	44.1	2.518	17.6	8.1	PHYS/1.3
15	PLAC	---	--	--	--	--	---
16	CONT	---	--	--	--	--	---
16	PLAC	---	--	--	--	--	---
17	CONT	---	--	--	--	--	---
17	PLAC	---	--	--	--	--	---
18	CONT	20.4 -104	34.0	-3.078	16.6	1.6	MOOD/0.3

Cont/-

Table 8-3 continued: -

18	PLAC	---	--	--	--	--	---
20	CONT	29.3 - 88	44.1	2.629	18.4	7.0	MOOD/1.1
20	PLAC	---	--	--	--	--	---
21	CONT	20.7 - 34.7	26.0	3.128	12.9	6.2	MOOD/1.0
21	PLAC	9.5	9.5	2.714	4.2	--	---
25	CONT	21.0 - 26.3	21.0	-2.436	8.2	9.4	PHYS/1.5
25	PLAC	14.4 - 17.9	17.9	3.056	8.7	6.2	MOOD/0.9
29	CONT	19.5 - 39.1	25.9	-2.976	12.3	6.0	MOOD/1.0
29	PLAC	---	--	--	--	--	---
30	CONT	---	--	--	--	--	---
30	PLAC	---	--	--	--	--	---
32	CONT	8.7	8.7	-3.030	4.2	--	---
32	PLAC	---	--	--	--	--	---
35	CONT	10.1	10.1	3.131	5.0	--	---
35	PLAC	10.8 - 14.8	14.8	-2.364	5.6	4.8	MOOD/0.8
36	CONT	17.0	17.0	-2.578	7.0	--	---
36	PLAC	18.0	18.0	2.051	5.9	--	---
37	CONT	21.6 -130	32.5	-2.885	14.9	0.7	MOOD/0.1
"	"	13.0 - 16.3	14.5	2.474	5.7	1.2	MOOD/0.2
37	PLAC	10.6 - 47.4	23.8	-3.010	10.4	24.6	MOOD/3.9
38	CONT	5.7 - 37.5	15.0	-3.088	7.36	9.0	PHYS/1.4
38	PLAC	8.7 - 70	17.5	2.732	7.6	5.8	PHYS/0.9
39	CONT	---	--	--	--	--	---
39	PLAC	---	--	--	--	--	---
44	CONT	---	--	--	--	--	---
44	PLAC	12.6 - 15.2	15.2	1.885	4.6	0	---
45	CONT	11.4 -114	28.5	2.964	13.4	0	---
45	PLAC	8.3 - 37.5	15.0	2.809	6.7		---
46	CONT	22.0 - 27.5	27.5	2.370	10.4	11.4	PHYS/1.8
46	PLAC	---	--	--	--	--	---
48	CONT	---	--	--	--	--	---

Cont/-

Table 8-3 continued: -

48	PLAC	---	--	--	--	--	---
49	CONT	5.3 - 23.8	23.8	-3.049	11.5	0	---
49	PLAC	---	--	--	--	--	---
50	CONT	---	--	--	--	--	---
50	PLAC	---	--	--	--	--	---

8-3-3 Presence Of Cyclicity In Control Cycles

For 22 of the 30 subjects there was clear evidence for menstrual cycle congruent cyclicity in mood and physical symptoms (table 8-2) ie., subjects 1, 2, 4, 5, 7, 8, 11, 14, 15, 17, 18, 20, 21, 25, 29, 36, 37, 38, 45, 46, 49, 50. For S32 and S48, there is marginal support for menstrual cyclicity in mood with the shortest period within an acceptable range of values, but the peak at a longer period. Menstrual cyclicity for physical symptoms in these subjects is supported. S35 shows the reverse pattern, with clear menstrual cyclicity for physical symptoms and the mood spectral density function overlapping with menstrual length periods but peaking at a shorter period of approximately 10 days.

For five subjects, the pattern of cyclicity is not so clear. While showing significant menstrual length cyclicity in physical symptoms, S10, S30 and S44 had significant mood symptom cyclicity at periods less than menstrual length. S16 shows the reverse pattern, with menstrual cycle congruent cyclicity present for mood, but very short period cyclicity evident for physical symptoms. While S39 showed no significant mood cyclicity within the menstrual range, she did so for shorter periods. The range of significant physical symptom cyclicity included menstrual cycle congruent periods, but the peak is displaced towards longer periods.

If both mood and physical symptoms need to be cycling significantly at approximately menstrual cycle length, then 22 out of the 30 subjects satisfy this requirement. If the requirement is for either to be cycling at around this period, then all are acceptable.

No subject showed evidence of line spectra characteristic of deterministic cycles but the small number of cycles means this would be unlikely. However the broad peaks found are characteristic of probabalistic cycles.

8-3-4 Retrospective Diagnosis

The adequacy of retrospective self-report of menstrual cyclicity in symptoms is confirmed. All subjects showed evidence of this in the spectral analysis of the prospectively collected data during the control phase.

8-3-5 Effect Of Treatment Expectations

Spectral density information suggests that 20 subjects were not greatly affected by the placebo preparation, which was given to alter expectations (S's 2, 5, 7, 8, 16, 20, 21, 25, 29, 30, 32, 35, 36, 37, 38, 44, 45, 46, 48, and 49). For these subjects there is clear evidence for continued significant cyclicity with periods congruent with the menstrual cycle. For subjects 4, 5, and 7, the peaks in the spectral density function were broader than previously observed. This probably reflected the fewer data points in placebo cycles for these subjects and the corresponding increase in bandwidth and decrease in sensitivity. Subjects 35 and 36 showed the opposite pattern with the spectral density peaks narrower during the placebo condition. This again is most likely a reflection of the increase in number of placebo data points and narrower bandwidth used for these subjects.

While having significant cyclicity in the range of menstrual cycle length, S's 4, 14, 15 and 17 showed shifts in peak spectral density value ie., S14 to shorter cycles for mood, S4 to longer cycles for mood and S's 15 and 17 to longer cycles for both mood and physical symptoms. Again the

impact of variation in number of data points may well be responsible.

Three subjects did not show evidence of mood related menstrual cyclicity in the placebo cycles, whereas they had in control cycles (S's 1, 10, and 39).

Three subjects with control cycle physical symptom cyclicity, did not show evidence of this in the placebo cycles (S's 11, 18, and 50).

An alterative way of assessing the impact of the placebo treatment is by looking at the degree of coherence between the symptom types. This analysis is discussed in 8-3-6.

8-3-6 Presence Of Other Than Menstrual Cyclicity

Many of the subjects exhibited significant cycles with periods outside the range of the menstrual cycle (table 8-2). A very short cycle, period around 2.4 days, exists for S1's mood scores under placebo. Mood cycles with a period of approximately 7 days were found in S's 10, 18, 20, 21, 36 and 44 under control conditions and in S's 5, 7, 18, 21, 29, 30, 35, 44 and 46 under placebo. For physical symptoms, similar weekly cycles existed for S's 10, 16, 20, 21, 49 and 50 under control conditions, and for S's 21, 49 and 50 under placebo. Longer cycles (which were still shorter than menstrual, ie., around 12-14 days) were found for mood in S's 10, 25, 30, 32 and 39 under control conditions, and for S 16 under placebo. For physical symptoms 12-14 day cycles were evident in S's 7 and 32 under control conditions, and S's 10 and 25 under placebo.

8-3-7 Relationship between psychological and physical symptoms

Seven subjects showed significant coherence between mood and physical symptoms for both control and placebo conditions

within the range accepted as being of menstrual significance (S's 2, 4, 7, 8, 37, 38 and 45). Significant coherence between mood and physical symptoms, for control cycles, was found in S's 1, 5, 11, 14, 15, 18, 20, 21, 29, 46 and 49, but this relationship was lost under placebo. No significant relationship between mood and physical symptoms was found for S's 10, 16, 17, 30, 39, 48 and 50. A significant relationship was found for periods shorter than those accepted as menstrual cycle-related for S's 25, 32, 35 and 36 within the control cycles. This short period coherence continued under placebo conditions for S's 25, 35 and 36, but was lost in S32. S44 showed no significant coherence in control cycles, but developed a short period coherence during placebo treatment.

8-3-8 Phase Relationships

These were interpreted where significant coherence and spectral density cyclicity existed. Data series which meet these requirements, had phase values at peak frequencies, equivalent to a half cycle delay between mood and physical symptoms. This delay was calculated by dividing the phase value by $2\pi f$, and applies to the one frequency. The resulting half cycle delay is a direct consequence of the opposite directions with which increasing severity is reflected in the devices constructed to measure the two domains. Therefore the two series approach synchrony.

The slope of the phase plot over the range of significant coherence gives the lead/lag relationship, independent of frequency, when divided by 2π (Gottman, 1981). This was able to be interpreted in 24 out of the 25 coherent series. One series showed evidence of a curvilinear pattern over the range of significant coherence and so was

not used. This analysis suggests that in sixteen of the series, mood leads by approximately one day. The remaining eight reflect physical symptoms leading with approximately the same delay.

8-4 DISCUSSION

The utility of spectral analysis in directly assessing cyclicity was demonstrated. The lack of evidence for the presence of deterministic cycles is not suprising given the variation in length of the menstrual cycles used in the analysis. It is clear that if more than one cycle is studied to reduce the risk of chance covariation between symptoms and the menstrual cycle, then the probabalistic nature of the data has to be considered. The alternative of standardising cycle length creates additional assumptions about the pacing of hormonal events.

The comparison between the analysis of variance approach and spectral analysis highlights the major strengths and weaknesses of the latter as an analytic technique. The strengths come from the individual focus and the direct assessment of cyclicity. Frequently, the challenge is in selecting subjects who in fact have the disorder. The extent to which future symptoms are predictable determines the validity of conclusions able to be drawn from intervention studies. Having a control group is no safeguard against including nonsufferers, nor does it prevent both the control and treated groups showing decreases in severity which are direct results of inconsistent symptom expression. This is not to suggest that subjects who manifest variable symptom expression do not have PMS; rather these subjects add to the existing confusion, and so should not be included. In using spectral analysis three criteria could be used to select a

sub group. Firstly, clear menstrual cyclicity in both mood and physical symptoms during the three control cycles is required. This produced 22 subjects in the present research. Secondly, subjects should not lose this cyclicity when treated with a placebo. This reduced the pool to 15 subjects. Thirdly, there should be significant coherence between the mood and physical symptom series. This further reduced the pool to 7 subjects. These are S's 2, 4, 7, 8, 37, 38, and 45. These three requirements are demanding, but would give rise to a subject population of known dimensions.

Another feature of the spectral analysis is the identification of significant cyclicities at periods shorter than the menstrual cycle. The weekly cycles give rise to speculation about the role of social events in determining negative symptoms. This is more difficult to explain with the approximately fortnightly cycles. However there are obvious limitations if symptoms are measured at a limited number of points during the cycle, particularly on one single occassion. It is possible that any choice of contrast period would be contaminated by such cycles.

The requirement that the mood and physical symptom series show significant coherence over the range of frequencies associated with the menstrual cycle is the most contentious of the three selection criteria. The discrimination on the basis of what symptom type is of predominant interest is arbitrary and difficult to justify on any theoretical grounds. It is possible that subjects showing one category of symptom but not the other constitute a homogeneous subtype. However the advantage of the coherence requirement is that it provides a more general criterion of homogeneity and thus fits the broad definition of PMS.

The limitations of spectral analysis are twofold. Firstly the large number of data points required is a major problem. Even though the number of points available in the present analyses ranged up to 123, this is insufficient. The length of the menstrual cycle requires in excess of this to fully explore the potential of this technique. If the lack of response to placebo was dropped from the selection procedure suggested above, the baseline length is still considerable. Another feature of this is that none of the series had zero power at f=0. This is possibly the result of trend but little slope is evident, and the lack of order effects within the analysis of variance mitigate against this. An alternative explanation is that the limited number of data points results in poor discrimination at short frequencies. This raises the possibility that long seasonal cycles are present. Given the extended period of data collection this is possible. The usual method of removing seasonal trends is differencing, but this risks removing the short frequency cycles associated with the menstrual cycle.

Secondly, spectral analysis does not provide a direct measure of severity. The series either show or fail to show significant menstrual cyclicity. This is a major disadvantage. Being able to detect a significant reduction in severity is useful in evaluating treatments.

In light of the joint advantages and individual disadvantages, the use of both approaches to the analysis of longitudinal data, is the most useful.

CHAPTER NINE - CONCLUSIONS

This chapter presents a summary of the findings and an appraisal of the shortcomings in the two studies. Where appropriate, alternative procedures are identified and suggestions for future research are proposed.

9-1 SUMMARY OF FINDINGS

9-1-1 Retrospective and Prospective Recording

Groups differing in retrospectively rated severity did not show significant variation in incidence. This was independent of whether incidence was calculated for mood-related or physical symptom-related PMS. It was also independent of which symptom type was present within any one cycle. These same groups, differentiated according to retrospectively rated severity did show significant differences in severity of mood symptoms when this was recorded prospectively. Further, these between-group differences in mood severity were specific to the premenstrual phase and did not occur in relation to scores at mid-cycle. There were no similar significant differences found for physical symptom severity.

The interview measures, taken at interview one, suggested that there was limited overlap between these measures and the subsequent symptom records. The most powerful predictor of these symptoms was the simple VAS rating of the previous month. The descending order from VAS1 to VAS6 suggests that accuracy could be a function of the amount of time being rated. The comparison between interview two and the symptom ratings from the previous three control cycles were similar, but showed a greater degree of overlap. This may have been function of increased

awareness of symptoms as a function of daily recording.

Interview one and two overlap to the extent of 30% of the total variance, with the Steiner scales being predominant. Interview three ratings compared with symptoms in the placebo cycles showed no overlap, with the VAS1(3) predicting best. The consistency of the Steiner scales with respect to all but the symptoms in placebo cycles suggests these may have been a function of a more constant feature of the subjects' perceptions such as Ruble's(1977) stereotypic beliefs.

9-1-2 Negative Expectations

An attempt was made to counter negative expectations by inducing positive treatment expectations via a placebo preparation. This decreased the incidence of mood-related but not physical symptom-related PMS. Where PMS was defined as either of these symptom types being present, predictably the placebo had no significant effect. Placebo was associated with an increase in premenstrual mood and the relative between-group severity differences were preserved. There was also a premenstrual decrease in physical symptom severity during placebo administration.

The interview two and three results showed no overlap. This supports the presence of a treatment effect and suggests that retrospective ratings are to some degree sensitive to actual events.

The spectral analysis suggested 21 subjects were unaffected, in the sense of retaining cyclicity during the administration of the placebo. Three subjects showed equivocal evidence of being affected, but this may have been the result of differing number of data points in the respective series. Three subjects showed an significant

effect on mood scores and while another three showed the same for physical symptom scores. Again this is in the sense of no longer showing evidence of significant cyclicity. With this technique it is difficult to quantify exact changes in severity.

9-1-3 Statistical Analysis

The use of an analysis of variance to detect changes in severity with treatment and the distribution of prospective symptom records with respect to retrospectively rated severity, was achieved best by using cycle phase as an independent variable. This produced two problems. Firstly, this style of analysis collapses across subjects thereby losing information about individual subjects. If there are good reasons for suspecting heterogeneity within subjects, this type of analysis is more difficult to interpret, especially where nonsignificant results are found. Secondly, using phase scores in this way provides only indirect evidence for cyclicity. It is possible by selecting different definitions of mid-cycle phase to either enlarge or minimise the amount of change found between it and the premenstrual phase.

A spectral analysis does provide a direct estimation of significant cyclicity or its absence. It also detects other than menstrual cycles which could induce confounding in other analytic techniques. The ability of bivariate spectral analysis to provide both a measure of the linear relationship and phase between the two series is a strength, particularly in the absence of any theoretical rationale for treating the two symptom types entirely separately. The ability to analyse the data from an individual subject is also useful for selecting subjects

showing cyclicity as well as measuring treatment effects at this level. The limitations of this technique are twofold. Firstly, considerable resources are required to collect sufficient data on sufficient subjects and to perform the analyses. Secondly, while the height of the spectral density peak is half the square root of the amplitude at that frequency, it is not clear what relationship exists between amplitude and clinical severity. To this extent it is difficult to evaluate and quantify significant decreases in severity.

9-1-4 Subject Selection

Although retrospective evaluation of mood severity did bear a significant relationship to prospectively measured symptoms, this by itself is insufficient reason for selecting subjects, because this relationship characterised neither incidence nor physical symptoms. Incidence is particularly important in light of the consistency of symptom expression needed to adequately evaluate any treatment strategy. To select a homogeneous subject population the parameters that are a result of spectral analysis should be used. These are (1) significant cyclicity within the menstrual range but not outside of this, (2) coherence between mood and physical symptoms, (3) the absence of any placebo effect. Screening by means of a simple VAS rating of severity of symptoms over the previous month would reduce the number of subjects in the first instance.

9-2 LIMITATIONS OF THE RESEARCH

9-2-1 Subject Selection

The subjects selected for inclusion represent a biased sample. Women prepared to keep daily records are likely to

be different from those who are not. The exclusion of those on oral contraceptives, while necessary, resulted in a less representative sample. No method of recruitment is ideal. That adopted in the present studies provided a sample of women who, during telephone interviews, convinced the interviewer that they suffered from PMS. Subjects were not required to be actively seeking treatment from General Practitioners or similar medical facilities. This raises questions concerning the seriousness of their disorder. However, most of the subjects were interested in treatment, and became involved in the sudies since they were not prepared to approach potentially unfriendly or neutral agencies to effect this. It is therefore difficult to gauge the actual severity of their symptoms.

9-2-2 Daily Diary

Although the daily diary was designed to collect prospective data, it in fact provided retrospective data, ie., the previous day. There was a considerable volume of data produced by the short term retrospective ratings used in the studies reported in this research. An alternative (between four and six ratings of current status each day) would have been impractical for both the subjects and researchers alike. In the interests of clarity the short term retrospective ratings have been referred to as prospective to distinguish them from the longer term retrospective ratings.

Using a sample of nonsufferers of similar age to the experimental population, the mood VAS scores correlated significantly with a validated general mood questionniare (MAACL). However these mood scales had the following shortcomings: (1) subjects complained about the lack of a

suitable scale for rating irritability. The deliberate reduction in direct relationship between the mood dimensions and well publicised PMS symptoms may have been overdone. (2) The request to rate the previous day was rated as being too difficult on some occasions by some subjects. Considerable diurnal variation made one rating seem detached from reality for those subjects. (3) The sexual interest VAS was inappropriate. It rated change rather than level and so was not included in the daily summary scores. It was clear that some subjects either misunderstood the format of the scale or showed steadily increasing or decreasing levels of sexual interest over the entire study.

The physical symptoms contained in the diary covered a smaller range of possibilities than for mood, and the type of scoring system was less flexible and may have been less sensitive to change.

The daily diary was the sole method of measuring symptoms. This reliance upon subject self report has been criticised as being inadequate. This criticism comes largely from those who seek to explain the lack of correlation between self report and so called "objective" indices of behaviour. There are poor grounds for expecting other than this. For example, the lack of congruence between physiologically recorded and self reported levels of sexual arousal has been explained in terms of differences in the respective processes rather than questioning the truthfulness of subjects. In the alcohol literature, where the behaviour under study is available to objective measurement, the accuracy of subject self report is verified (Sobell & Sobell, 1978). An alternative

strategy would be to gather confirmatory ratings from a spouse or close companion, as has been attempted with headache pain (Kazdin, 1977). The difficulties with this are; (1) there is a problem in determining which is veridical if the separate ratings do not correspond, and (2) there is some evidence to suggest that even close associates are not able to accurately determine mood state (Irwin et al., 1979).

One unfortunate aspect of the scoring procedure adopted for the daily diary was the scoring of an increase in feelings of well being for mood and physical symptoms, in opposite directions. The visual interpretation of phase would have been enhanced if these had been in the same direction.

9-2-3 Summary Scores

The summation of all VAS scales into a single mood score was necessary to manage the considerable volume of data produced. However, this results in minimising the position of a subject showing extreme variation on only one scale and little change upon the others.

The use of menstrual days five to fourteen as the midcycle phase, was a large period in contrast to premenstrual scores. It is possible that in short cycles ovulatory disturbance was inadvertantly included whereas with long cycles this would not be the case. This could have induced a bias against long cycles if the ovulatory change was characterised by transient increases in mood.

9-2-4 Length of Recording

The ideal length of records is at least six cycles. Baseline and intervention would therefore extend over five to seven months. The consequences would be major advantages

for the statistical analysis particularly by aiding resolution in the shorter frequencies and assisting the discrimination of menstrual related cyclicity from longer periods or trend. It would also avoid the confusion arising as a result of inconsistent symptom expression across months. It does however induce potential seasonal variations and expose the subjects to many more social and psychological stressors, as well as being demanding thus potentially further biasing the final sample.

9-3 SUGGESTIONS FOR FURTHER RESEARCH

There are four major classes of further research needed.

(1) The empirical investigation of subtypes, particularly the differentiation between irritability/hostility and predominantly depression/dysphoria as major symptoms. This would involve reducing the emphasis upon biological verses psychological subtypes that has been explicit in much previous research, and the instead increasing the emphasis upon accurate identification and the delineation of treatment-subtype interactions.

(2) Implied in (1), but of critical importance is the need to improve procedures for identifying and selecting subjects, and the methods for analysing the prospective data. The procedures for subject selection, measurement and analysis, suggested by the research reported in this thesis would assist both the rational evaluation of treatments and the further exploration of subtypes. An additional method of analysis which is ideally suited to evaluating treatment effects is time domain modelling. The intensive analysis of multiple data series, involving a number of the biochemical

substances proposed as causative as well as prospective symptoms, could be usefully analysed using both frequency and time domain techniques.

(3) Limitations in the execution of the research reported here suggest some smaller topics of interest. The importance of consistent expression of symptoms is reflected in the need to investigate accuracy of retrospective self report of incidence. It would also be valuable to investigate the relationship between self-reported symptoms and the reports of significant persons in the subjects' enviroment. This would also have implications for the debate over what degree of severity warrants treatment.

(4) The development and evaluation of treatment derived from a psychological perspective, such as self management involving cognitive strategies, has not yet been attempted. This is consistent with the reduction of emphasis on the arbitrary distinction between psychological and biological symptoms suggested in (1) and could serve to highlight interrelationships.

Ultimately the value of the research reported in this thesis will be determined by the degree to which it is used. As always, it marks a beginning rather than an end.

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Appendix 1 - Daily Diary

Date ..... Name: .....

Weight today (before dressing) .....

Did you take any pills or medicine in the last 4 days .....

If you did, what was the name of the medicine (or pill) .....

and the dose ..... and the times taken .....

Below are some statements concerning your feelings. Please put a cross at the position which is closest to the way you felt.

Yesterday

1. How happy were you? happy — unhappy
2. How tired did you feel? exhausted — energetic
3. How confident did you feel? confident — hopeless
4. How tense or worried were you? very tense — calm & relaxed
5. How did you feel towards other people? friendly — hostile
6. How difficult was it to concentrate? difficult — easy
7. How easy was it to get things done? easy — awful
8. Was there a change in level of sexual interest? Decrease — Increase

---

Next come some questions. Please tick the correct box.

		Yes	No
(i)	Did your period start?		
(ii)	Did you have period pains?		
(iii)	Were you menstruating?		

Some more questions. Please tick the box that applies best to you.

		No	Yes	
			Mild	Severe
(a)	Were your breasts tender?			
(b)	Did you feel bloated?			
(c)	Were you constipated?			
(d)	Did you have a headache?			
(e)	Did you have any food cravings?			

Finally is there anything else you would like to say about yesterday.

_____

_____

_____

_____

Appendix 2 - Steiner Self Rating Scale

SELF RATING SCALE FOR PREMENSTRUAL TENSION SYNDROME

Name: _____ Date: _____

Instructions: The following questions are concerned with the way you feel or act today (or the way you felt or acted during the week).

Please answer ALL questions by circling YES or NO as indicated.

1.	Do you find yourself avoiding some of your social commitments	YES NO
2.	Have you gained 5 or more pounds during the past week?	YES NO
3.	Is your co-ordination so poor that you are unable to use kitchen utensils, garden tools or unable to drive?	YES NO
4.	Do you feel more angry than usual?	YES NO
5.	Do you avoid family activities and prefer to be left alone?	YES NO
6.	Do you doubt your judgement or feel that you are prone to hasty decisions?	YES NO
7.	Do you feel more irritable than usual?	YES NO
8.	Is your efficiency diminished?	YES NO
9.	Do you feel tense and restless?	YES NO
10.	Do you feel a marked change in your sexual drive or desire during the last week. (If YES, is it increased or decreased?	YES NO
11.	Are your present physical symptoms causing so much pain and discomfort that you are unable to function?	YES NO
12.	Have you recently cancelled previously scheduled social activities?	YES NO
13.	Do you feel as if you were unable to relax at all?	YES NO
14.	Do you feel confused?	YES NO
15.	Do you suffer from painful or tender breasts?	YES NO
16.	Do you have an increased desire for specific kinds of food (e.g.cravings for sweets, chocolate, etc.)?	YES NO
17.	Do you scream/yell at family members'(friends, colleagues) more than usual? Are you "short-fused"?	YES NO
18.	Do you feel sad, gloomy, and hopeless most of the time?	YES NO
19.	Do you feel like crying?	YES NO
20.	Do you have difficulty completing your daily household/job routine?	YES NO
21.	Was there a marked change in your sexual drive with definite change in your sexual behaviour during the last week?	YES NO
22.	Do you find yourself being more forgetful than usual or unable to concentrate?	YES NO
23.	Do you happen to have more "accidents" with your daily housework/job (cut fingers, break dishes, etc.)?	YES NO
24.	Have you noticed significant swelling of your breasts and/or ankles and/or bloating of your abdomen?	YES NO
25.	Does your mood change suddenly without obvious reason?	YES NO
26.	Are you easily distracted?	YES NO
27.	Do you think that your restless behaviour is noticeable by others?	YES NO
28.	Are you clumsier than usual?	YES NO
29.	Are you obviously negative and hostile towards other people?	YES NO
30.	Are you so fatigued that it interferes with your usual level of functioning?	YES NO
31.	Do you tend to eat more than usual or at odd irregular hours (sweets, snacks etc.)	YES NO
32.	Do you become more easily fatigued than usual?	YES NO
33.	Is your handwriting different (less neat than usual)?	YES NO
34.	Do you feel jittery or upset?	YES NO
35.	Do you feel sad or blue?	YES NO
36.	Have you stopped calling or visiting some of your best friends?	YES NO

Below are two statements concerning premenstrual tension syndrome. Please put a cross closest to the position you consider best describes your symptoms.

1. How severe were your PMT symptoms this last month?

absent _____ very severe

2. How severe were your PMT symptoms over the past six months?

absent _____ very severe

Appendix 3 - Steiner Observer Rating Scale

RATING SCALE FOR PREMENSTRUAL TENSION SYNDROME

Name: _____ Rater: _____ Date: _____

Circle the most appropriate score for each item:

1. Irritability-Hostility (0-4)

(Irritable, hostile, negative attitude, angry, short-fused, yelling & screaming at others)

0. Not irritable.
1. Doubtful, trivial. Not reported without direct questioning.
2. Mild, Occasional outbursts of anger and hostile behaviour. Spontaneously reported.
3. Moderate, Irritable behaviour evident. Frequent outbursts.
4. Severe. Affects most interactions between patient and significant others.

2. Tension (0-4)

(Tense, restless, jittery, upset, high-strung, unable to relax)

0. Not tense.
1. Doubtful, trivial.
2. Mild. Reports occasional tension.
3. Moderate. Tense, jittery, unable to relax. Restless behaviour evident.
4. Severe. Constantly tense and upset.

3. Efficiency (0-4)

(Decreased efficiency, easily fatigued)

0. No disturbance.
1. Doubtful, trivial.
2. Mild. Somewhat reduced efficiency.
3. Moderate. Easily fatigued, gets much less done than usual.
4. Severe. Fatigue causes serious interference with functioning.

4. Dysphoria (0-4)

(Dysphoric mood, distinguish from depression)

0. Not dysphoric.
1. Somewhat blue, sad. Elicited only on direct questioning.
2. Mild dysphoric and labile mood, spontaneously reported.
3. Marked spontaneous emotional lability; occasional crying; feelings of loneliness.
4. Severe, obvious and persistent.

5. Motor Co-ordination (0-4)

(Clumsy, prone to accidents, lowered motor co-ordination)

0. No disturbance.
1. Doubtful, trivial.
2. Mild clumsiness, feels awkward.
3. Moderate. Frequent "accidents".
4. Severe impairment in motor co-ordination, e.g. unable to write properly, sew, or unable to drive.

6. Mental - cognitive functioning (0-4)

(Forgetful, poor concentration, distractable, confused, lowered judgement)

0. No disturbance.
1. Doubtful, trivial.
2. Mild. Slight forgetfulness and distractability.
3. Moderate. Performance impaired by poor concentration, cognitive disorganisation, forgetfulness, etc.
4. Severe. Marked deterioration in cognitive capacity, poor judgement, leading to regrettable decisions.

cont/-

Appendix 3 continued: -

2.

Eating habits (0-2)

0. No change.
1. Mild increase in food intake, eating at odd, irregular hours, mostly snacks and sweets.
2. Obvious, marked increase. Uncontrollable cravings for sweets, chocolate, etc.

Sexual drive and activity (0-2)

0. No change.
1. Mild but consistent increase or decrease in sexual drive, desire, libido.
2. Marked change in sexual drive with definite change in sexual behaviour.

Physical symptoms (0-4)

(Painful or tender breasts; swelling of abdomen, breasts, ankles, or fingers; water retention; weight gain; headaches, low-back pain etc.)

0. No physical symptoms.
1. Doubtful or trivial.
2. Mild. Some symptoms, increased awareness of bodily changes.
3. Moderate. Obvious changes and complaints.
4. Severe. Physical symptoms are incapacitating. Pain and discomfort. Marked water retention and edema. Weight gain more than 5 lbs.

10. Social impairment (0-4)

(Avoidance of social activities and interactions with family, at home, at work, at school, etc.)

0. No social impairment.
1. Doubtful, trivial.
2. Mild avoidance of social activity.
3. Moderate but obvious impairment of social activity, mainly noticeable at home and with family.
4. Severe. Marked impairment of most social interactions including at work or school. Withdrawal, isolation.

Total score: .....

Appendix 4 - VAS at Third Interview

Treatment effectiveness:

Overall

very effective — not effective

First month

Second month

Third month

Stress level (over last 3 months)

very stressed — little stress

Willingness to participate in future treatment trials

very happy to — unwilling

How distressing were your PMT symptoms

First month

very — not at all

Second month

very — not at all

Third month

very — not at all

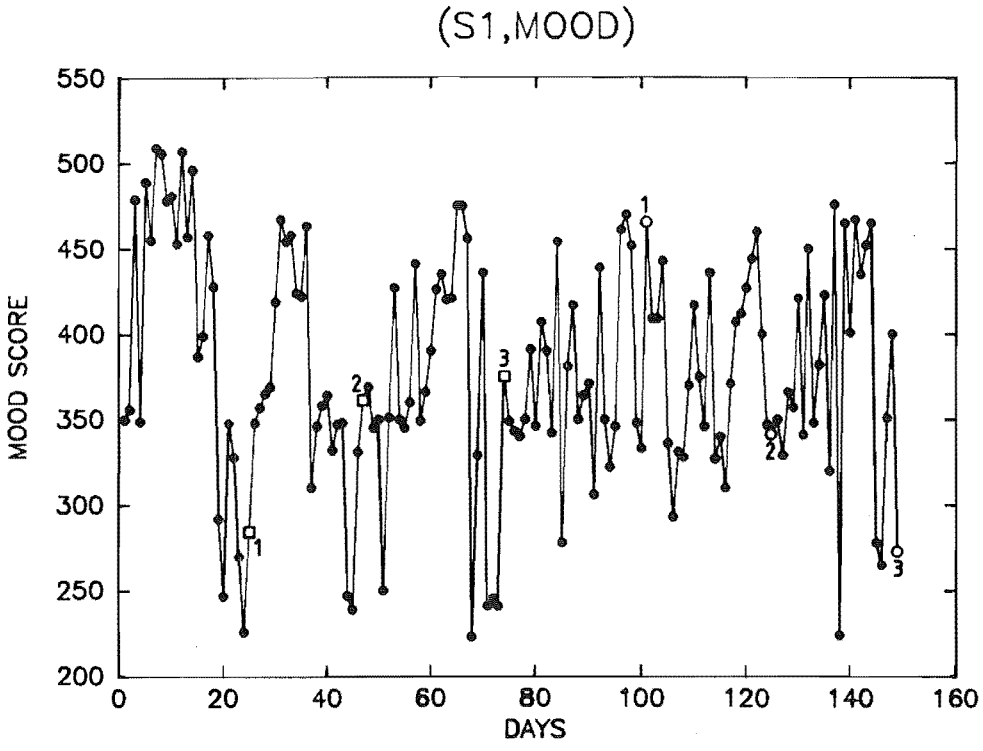
Overall

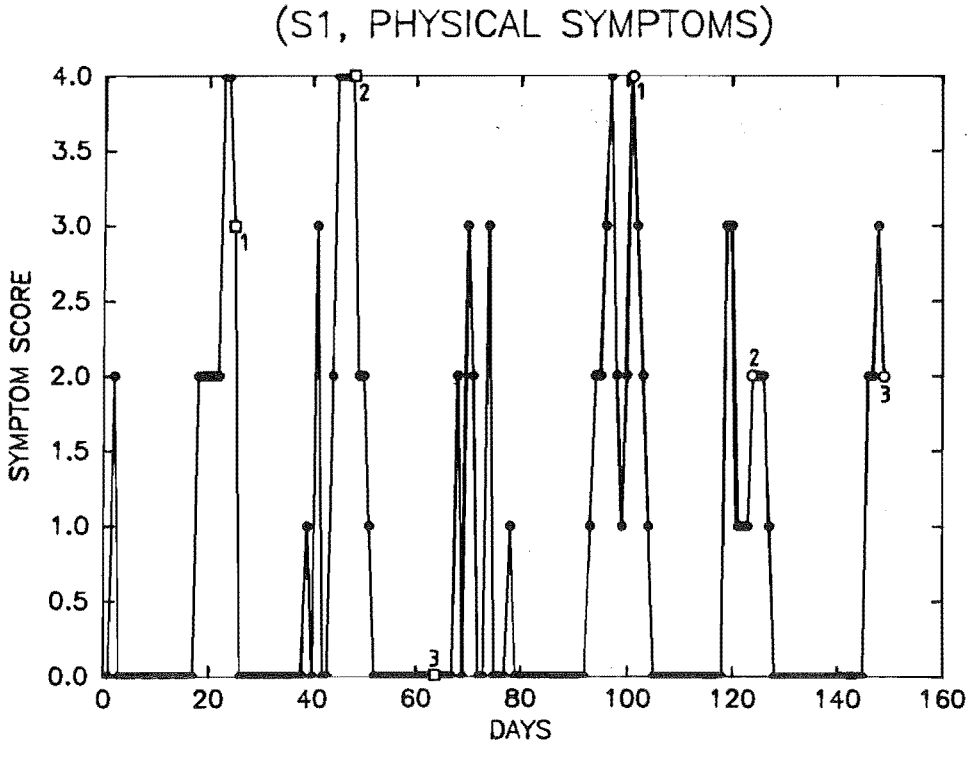
very — not at all

Appendix 5

Mood and Physical Symptom scores for Control and Placebo Cycles for Each Subject

Appendix 5 continued: -





□ = Control cycle 1 (etc)

○ = Placebo cycle 1 (etc)

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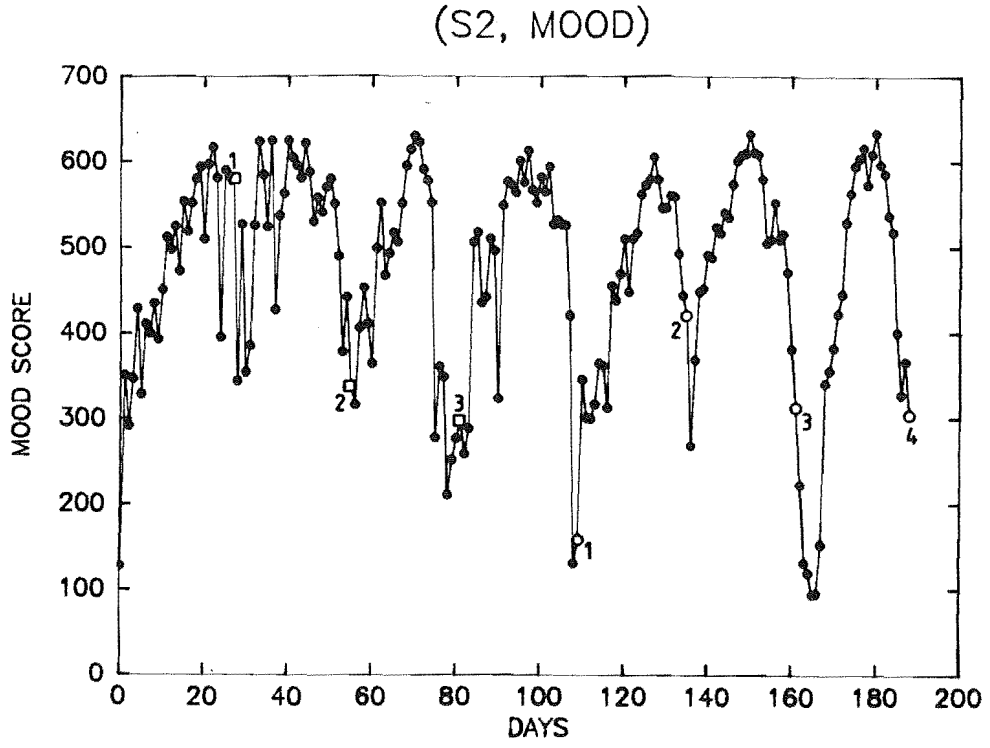

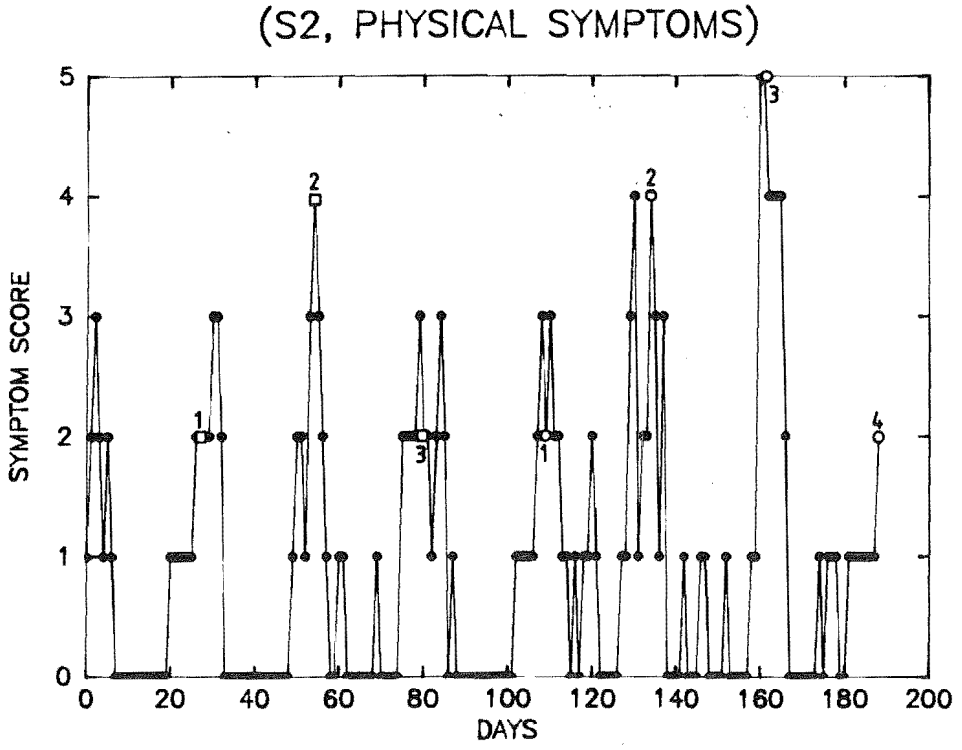

□ = Control cycle 1 (etc)

○ = Placebo cycle 1 (etc)

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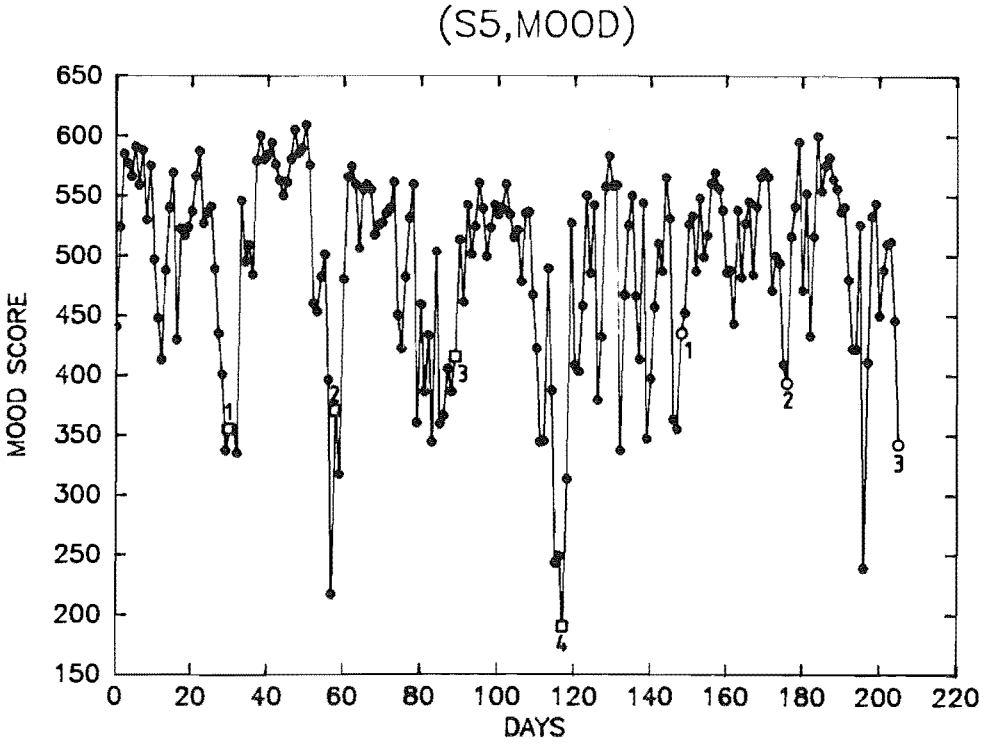

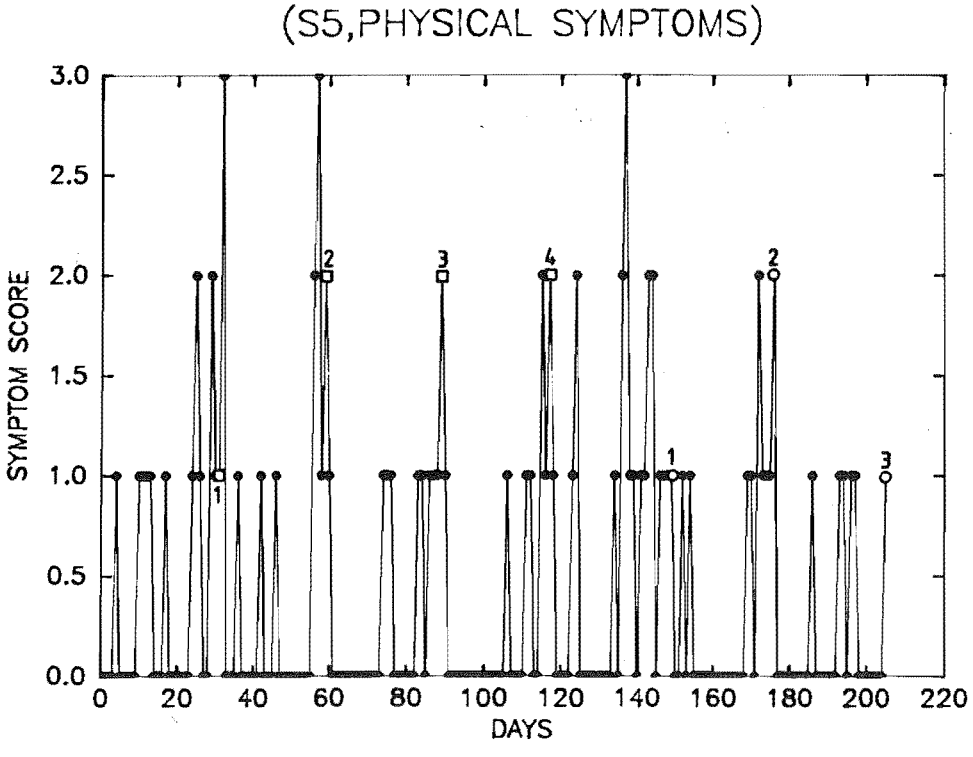

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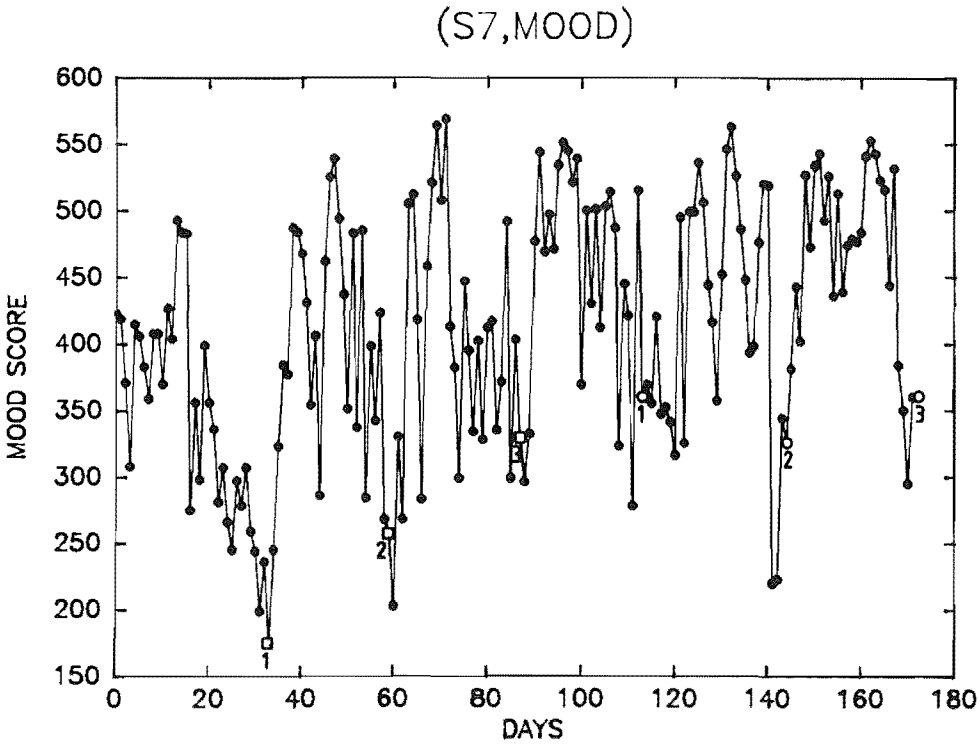

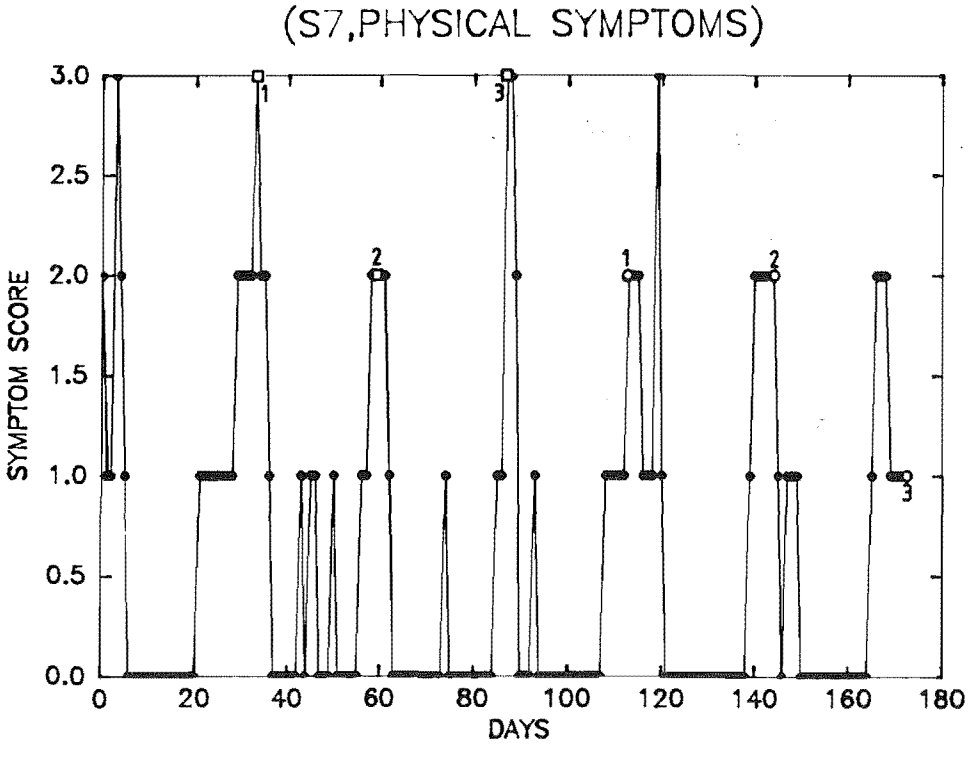

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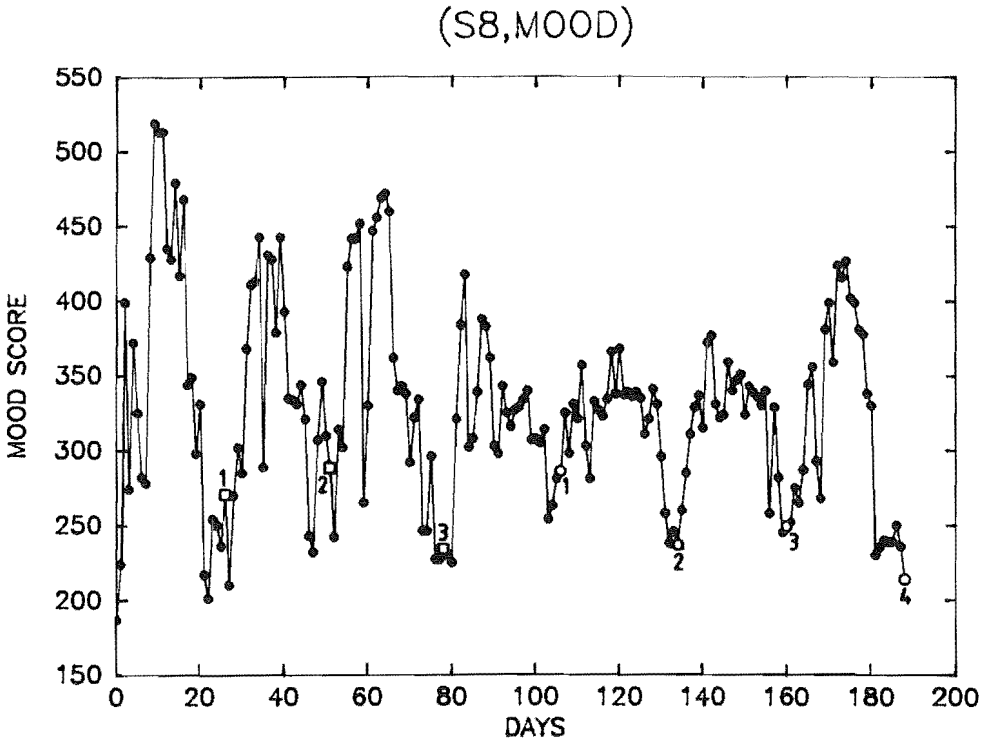

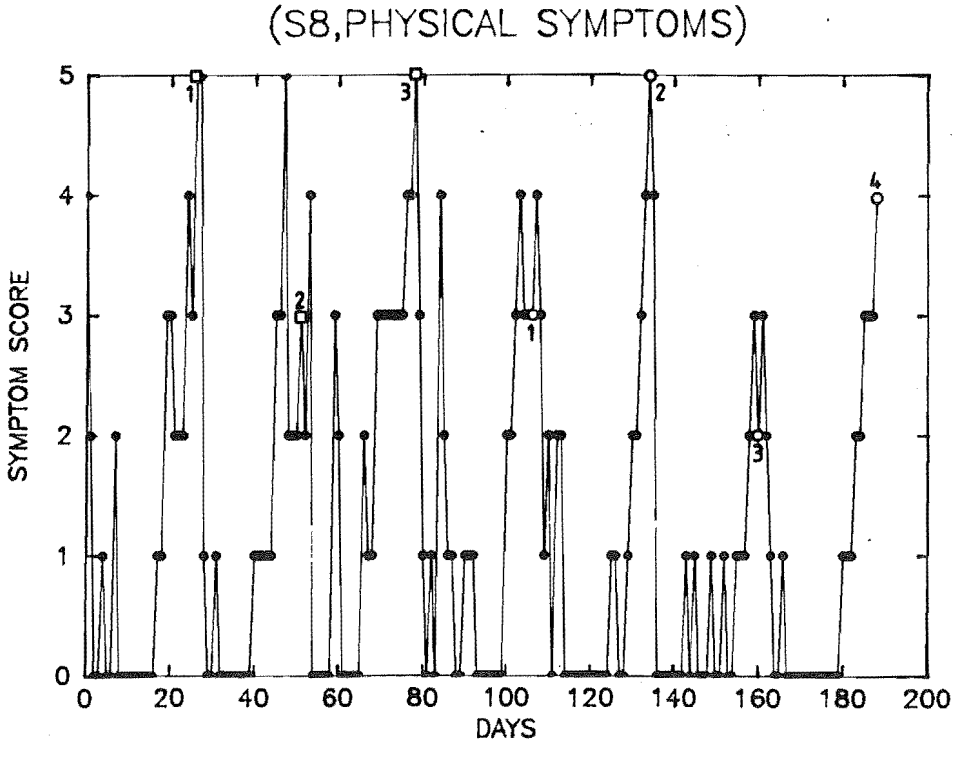

□= Control cycle 1 (etc)

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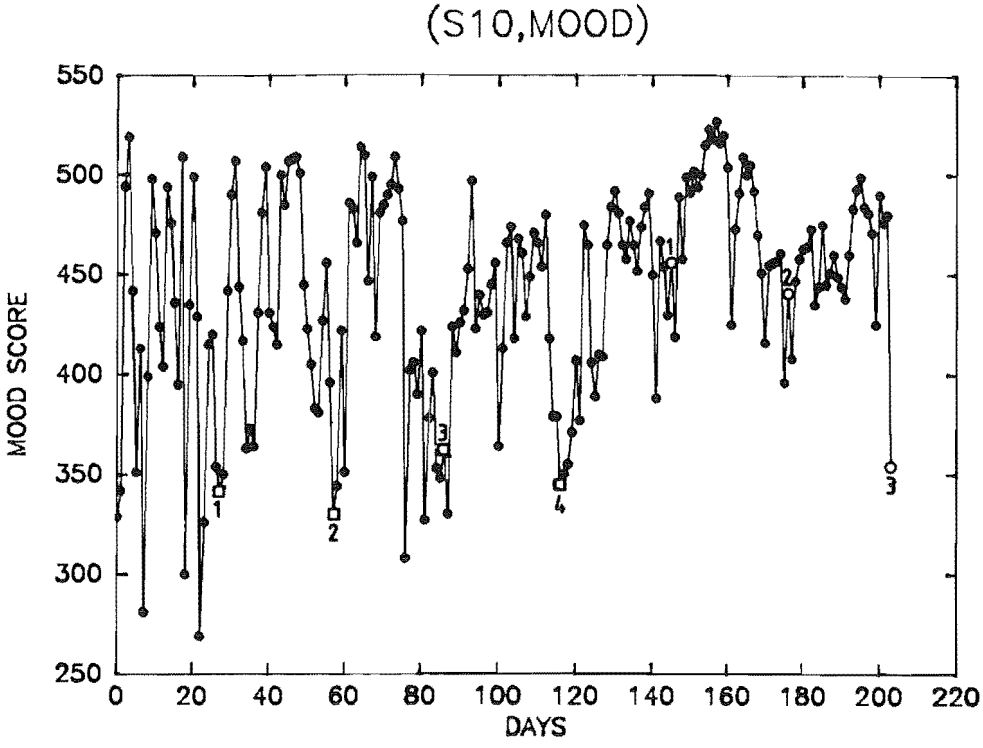

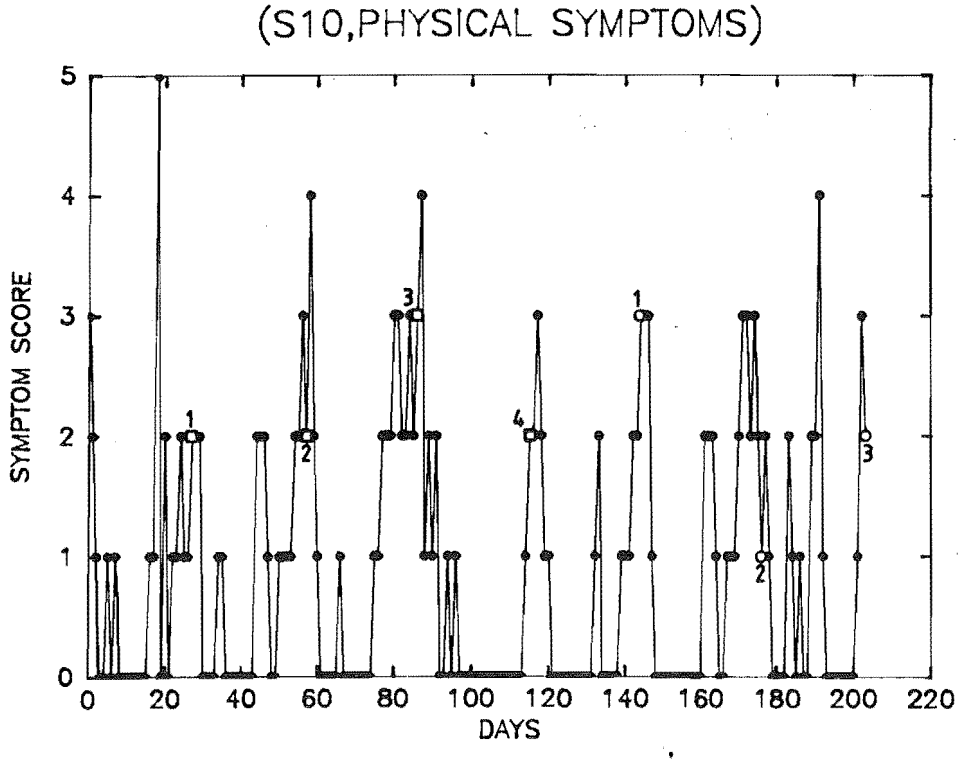

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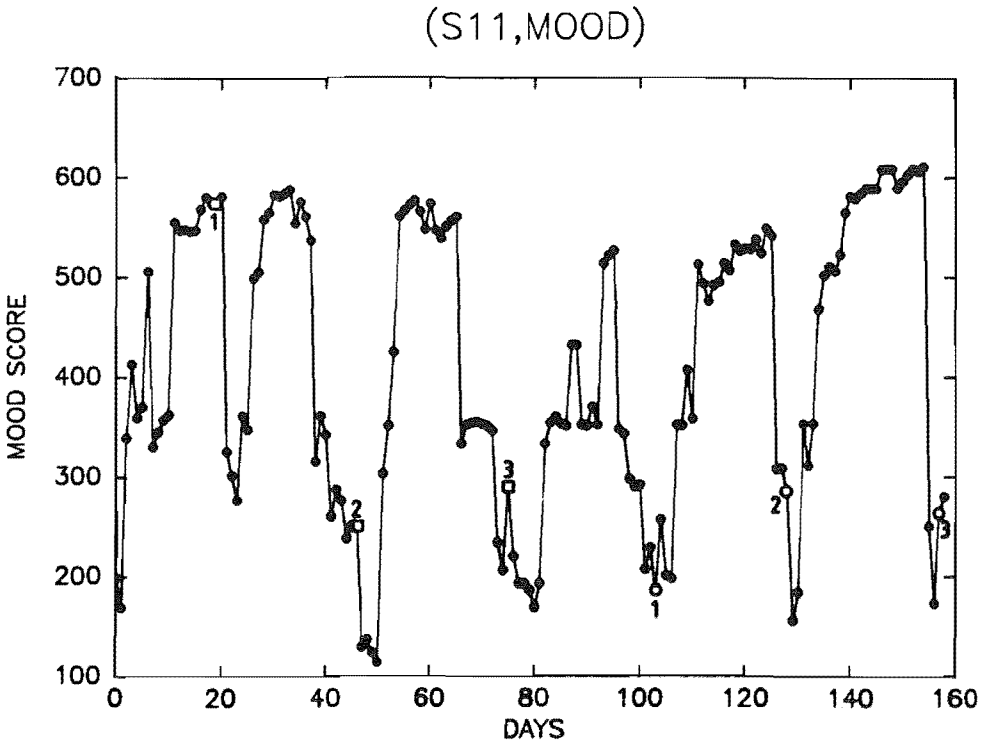

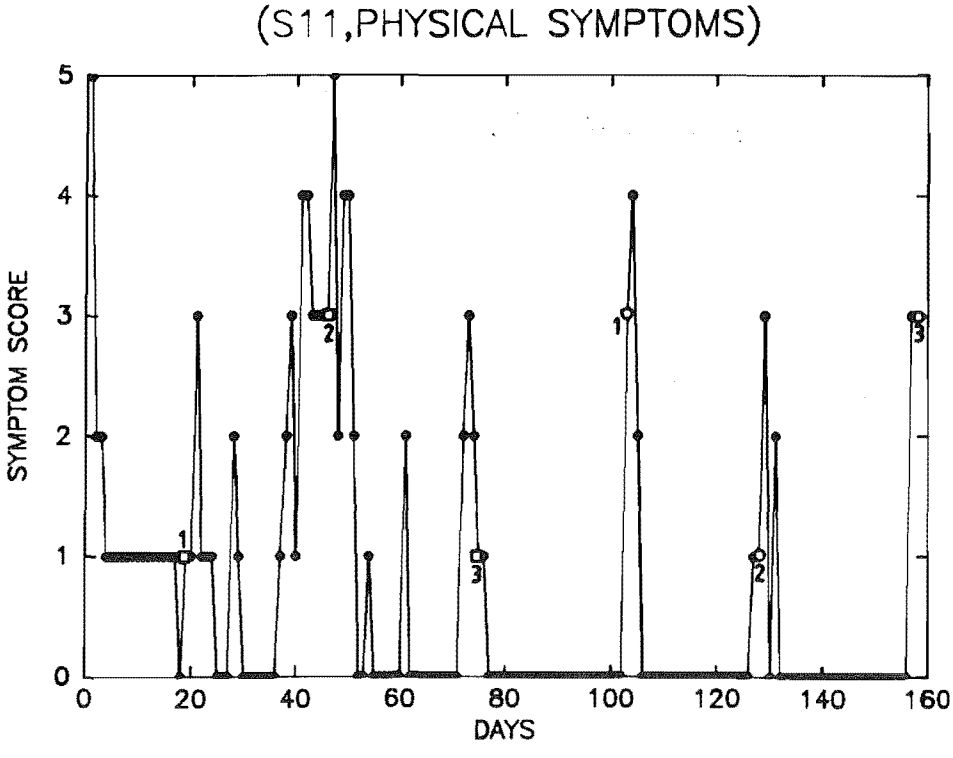

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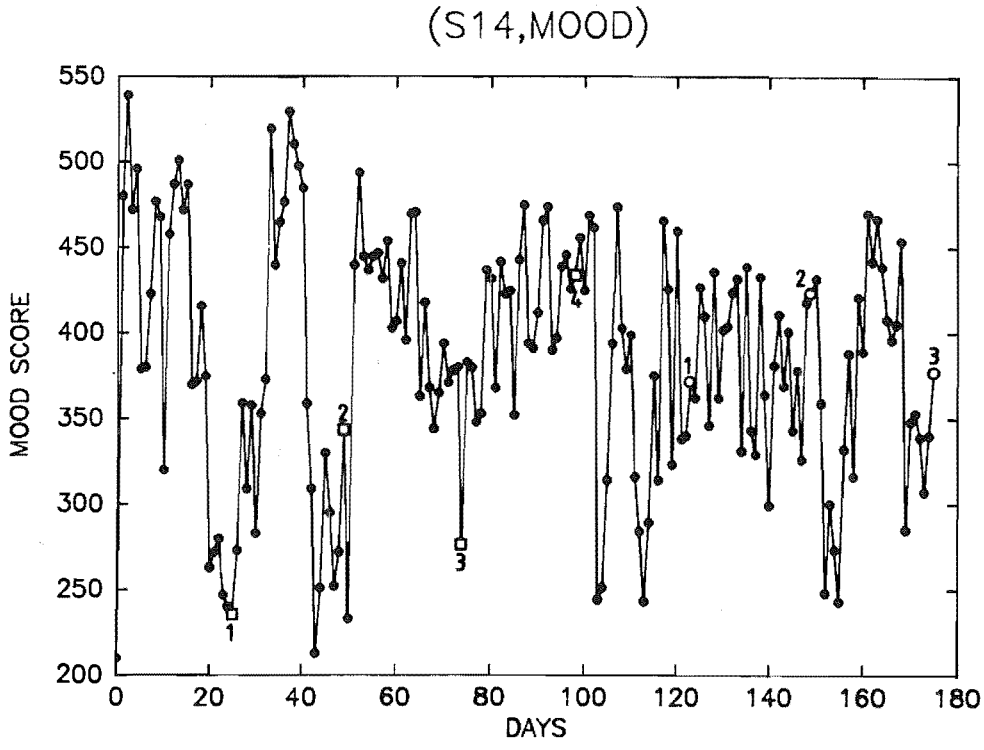

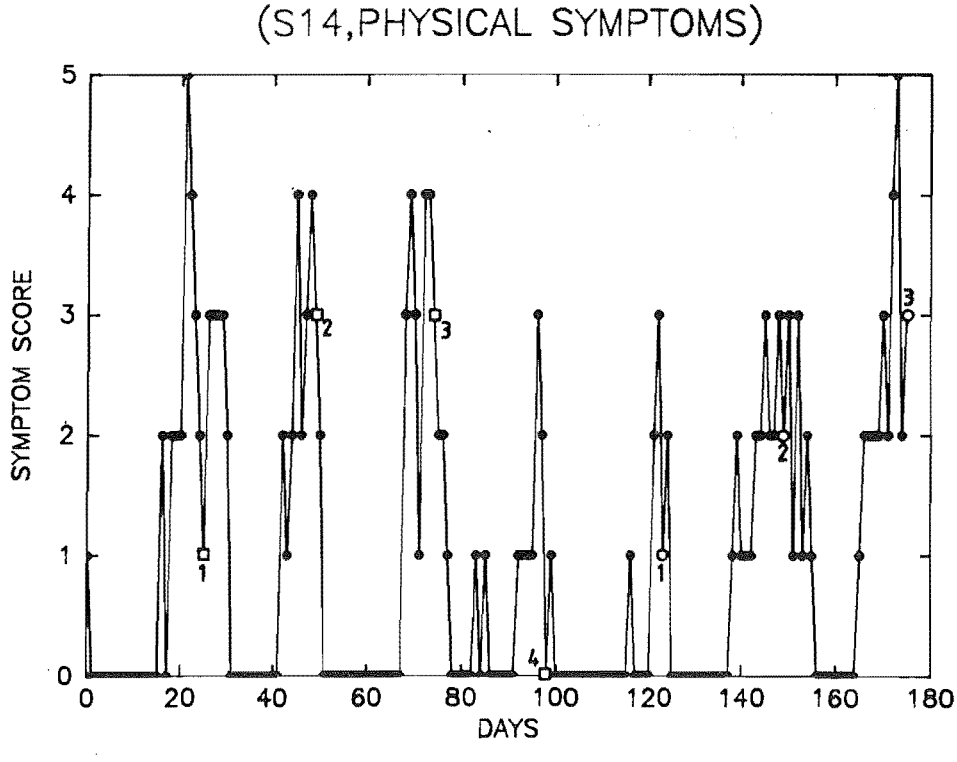

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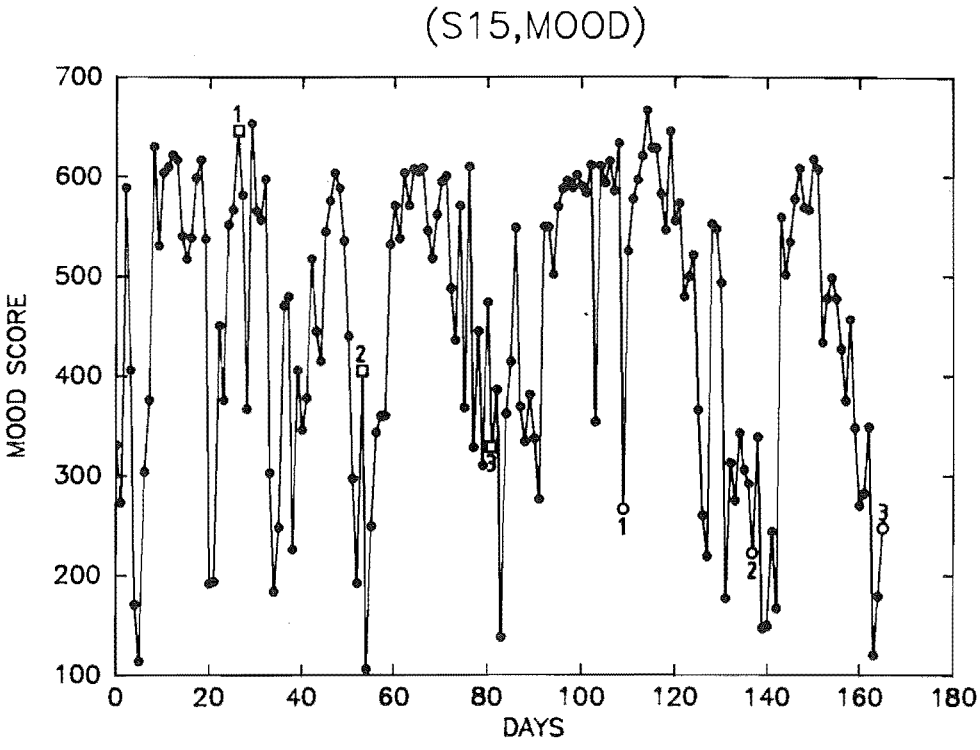

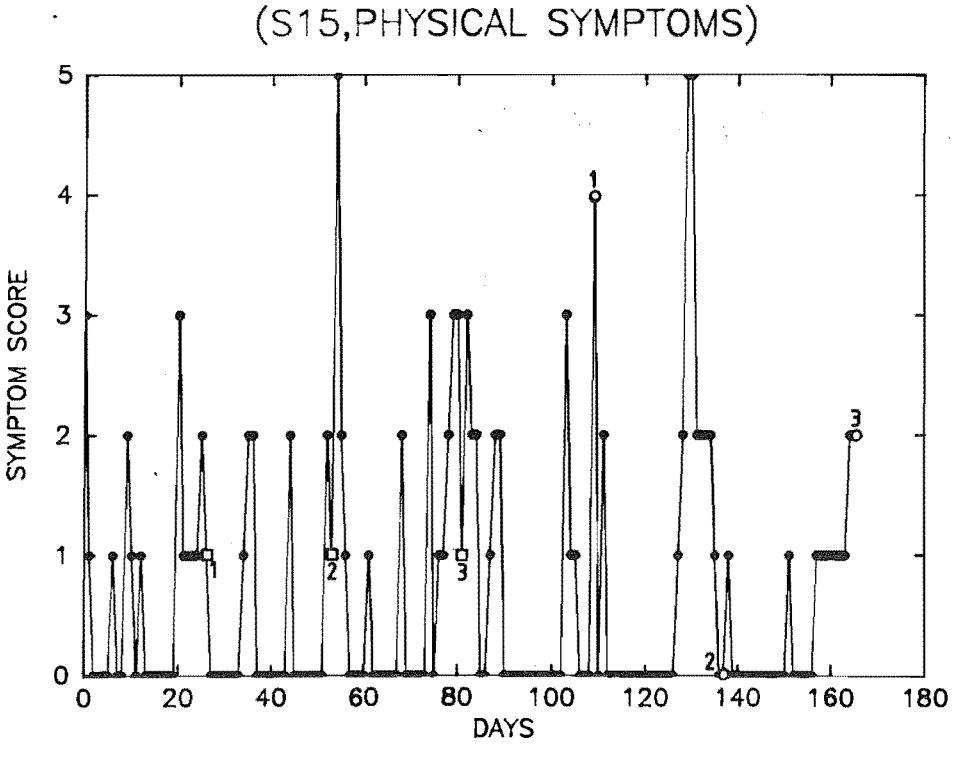

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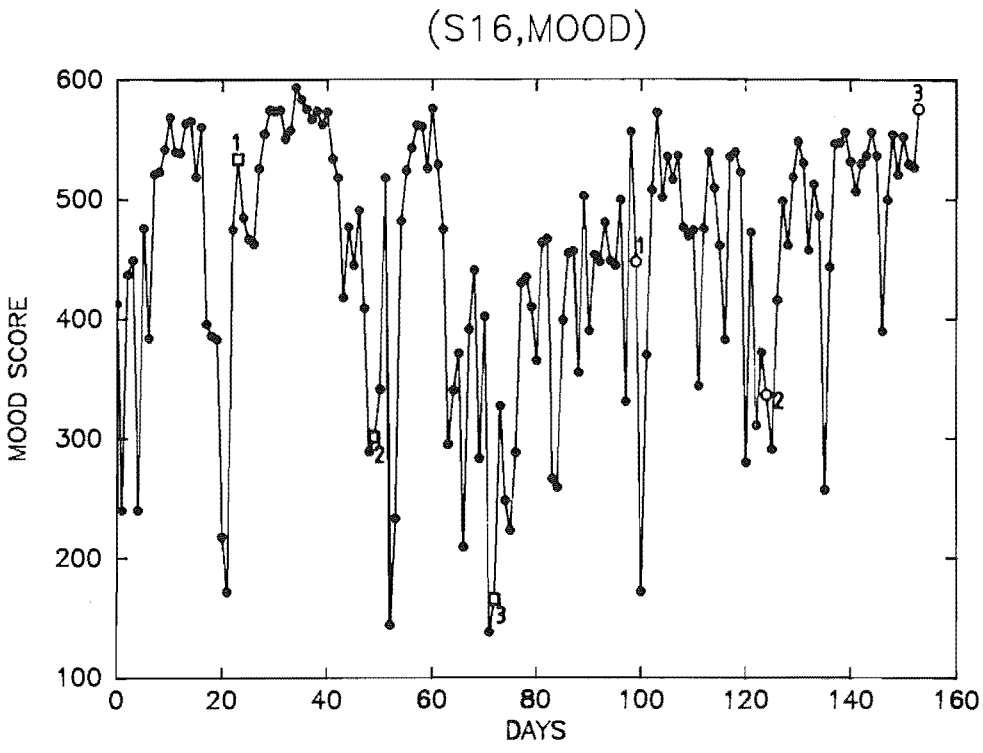

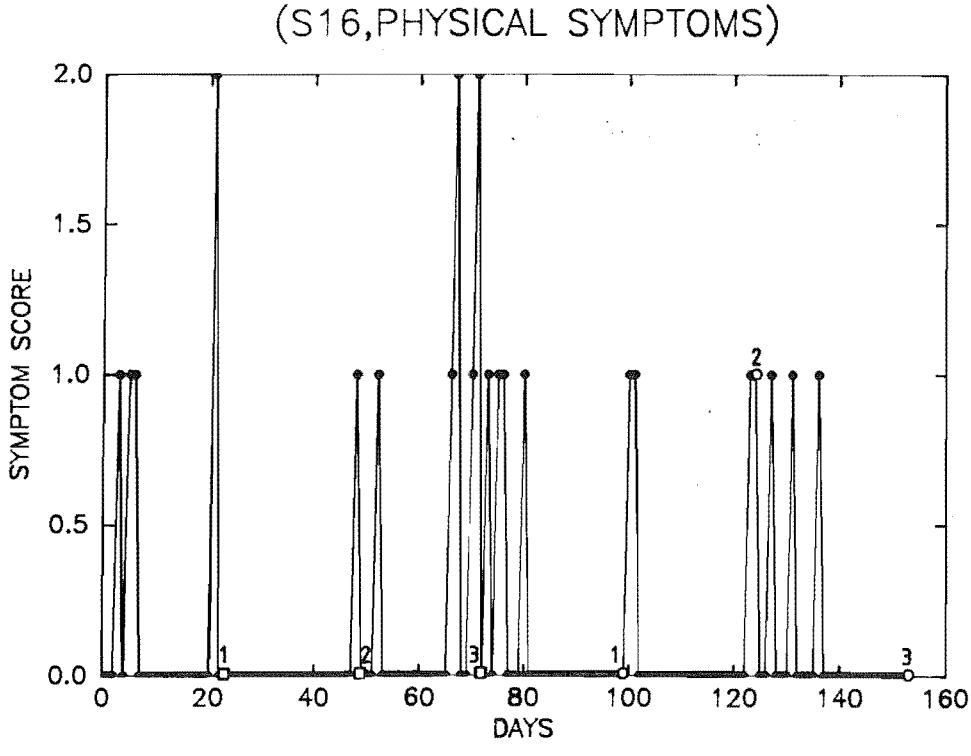

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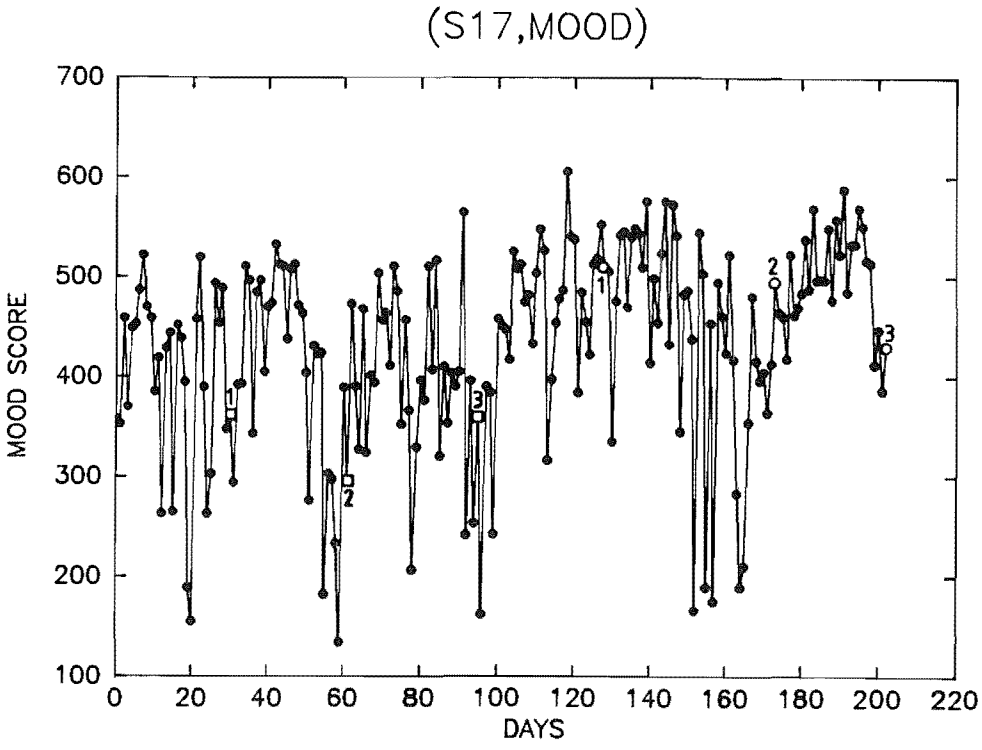

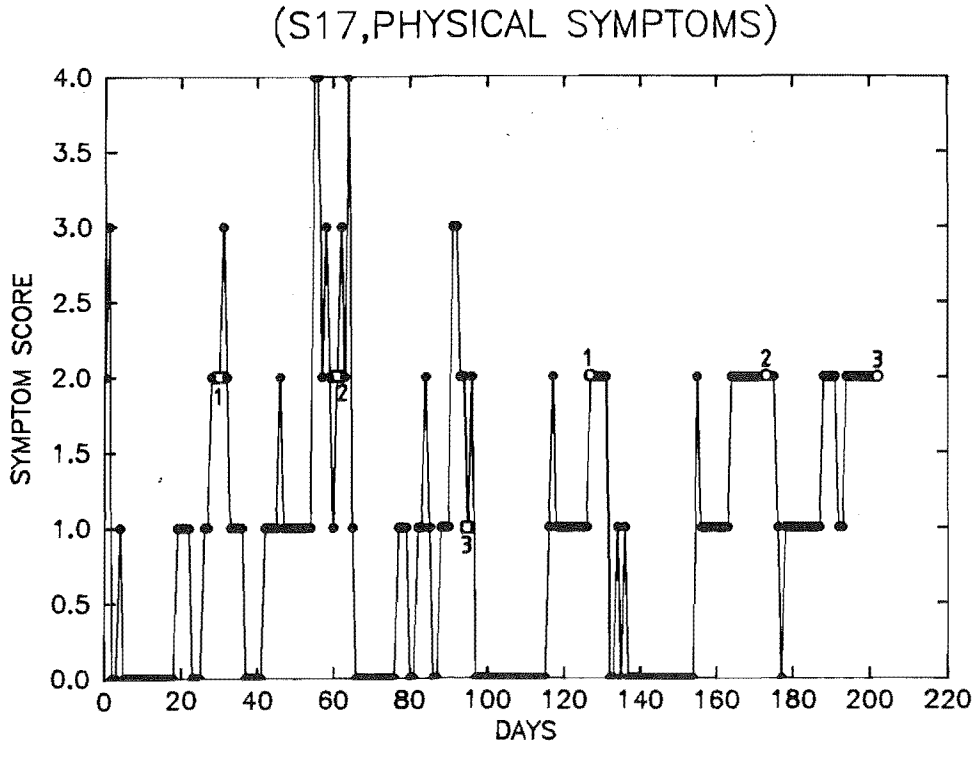

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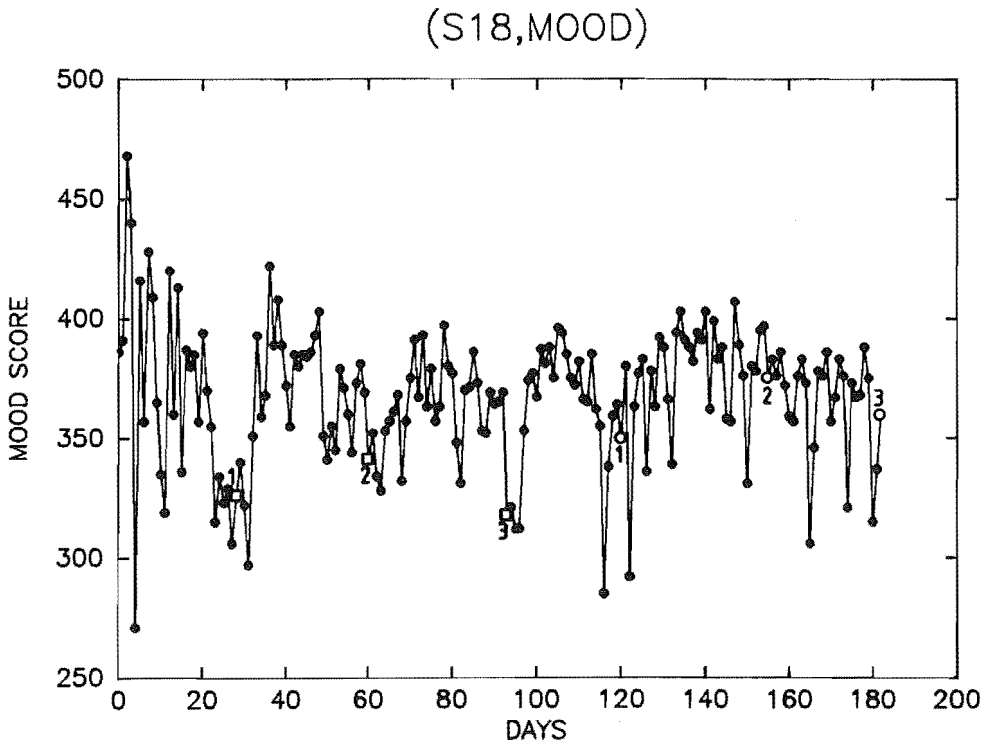

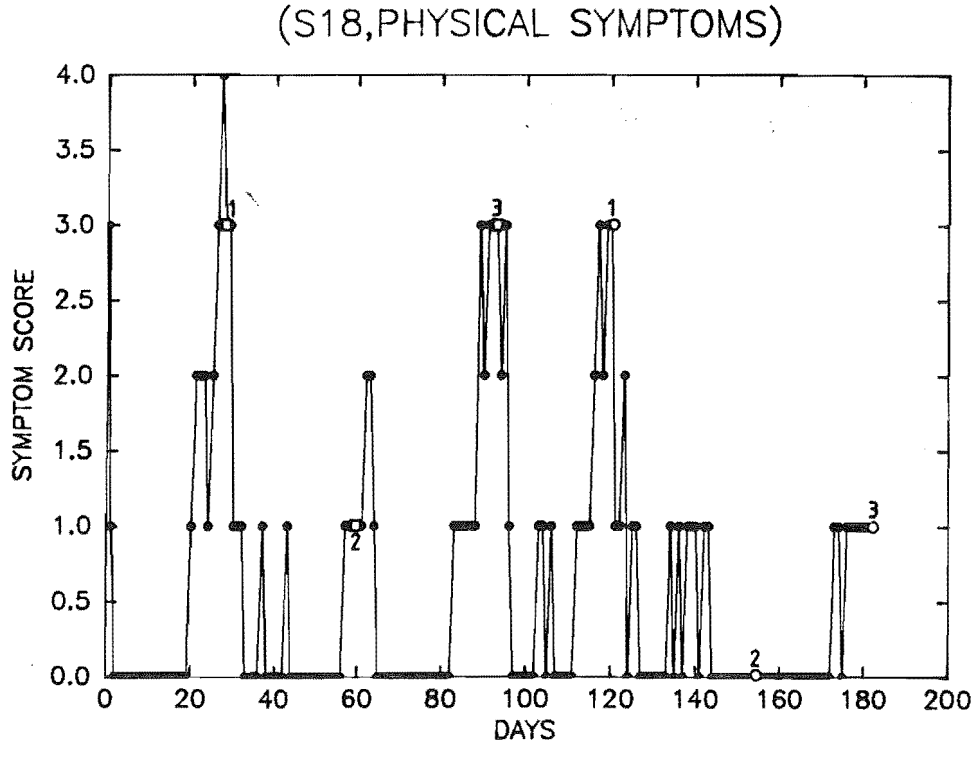

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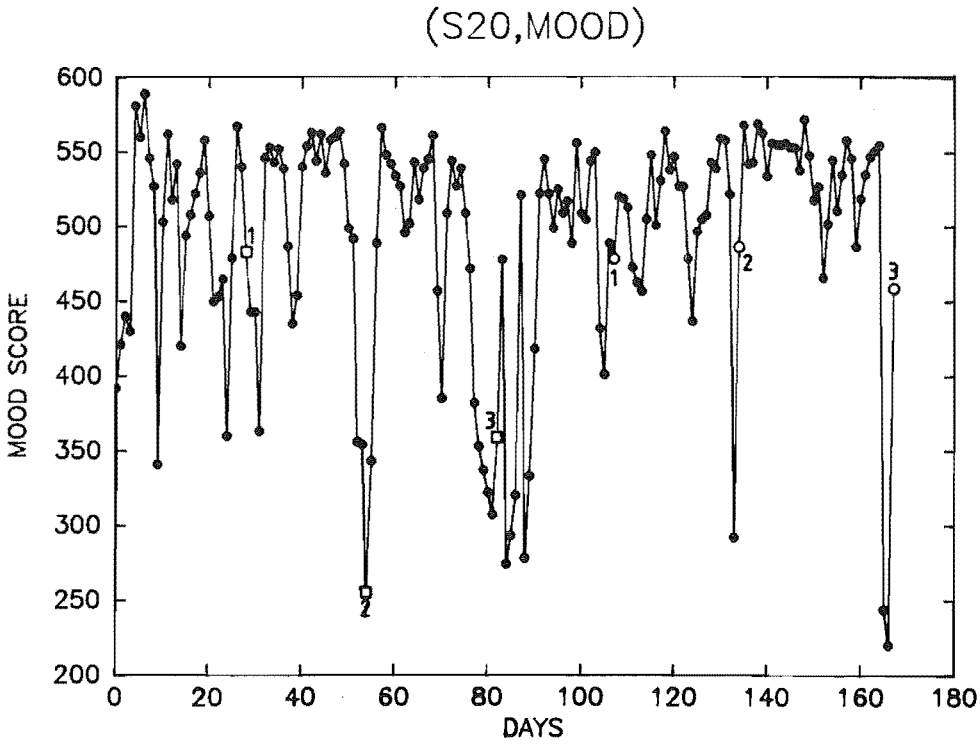

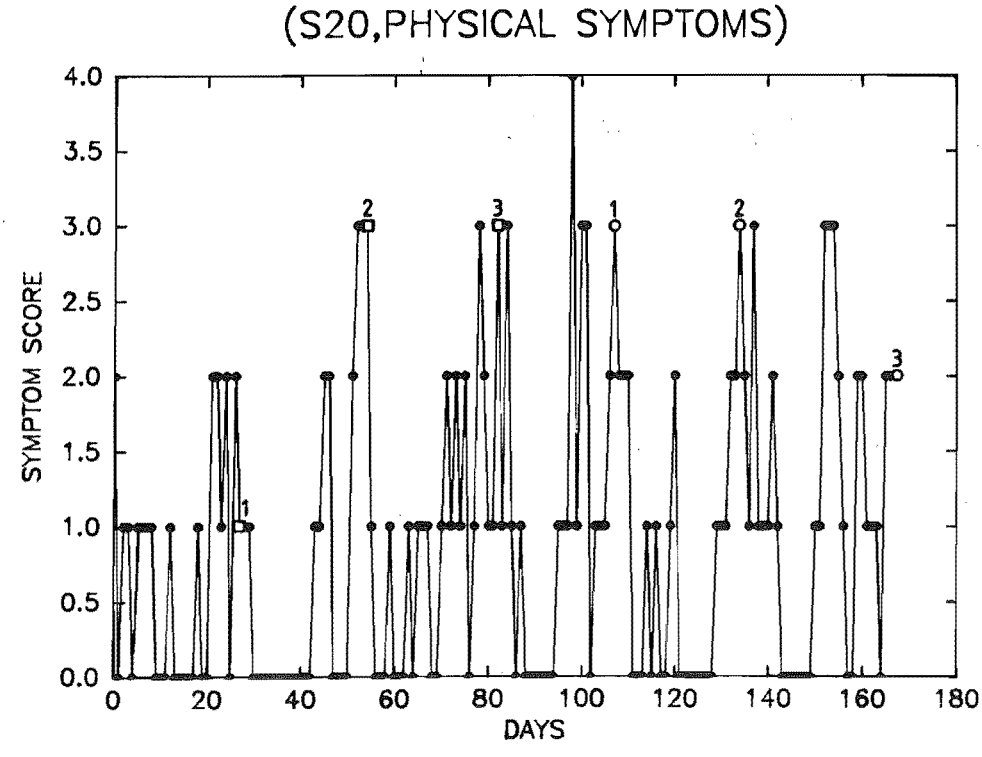

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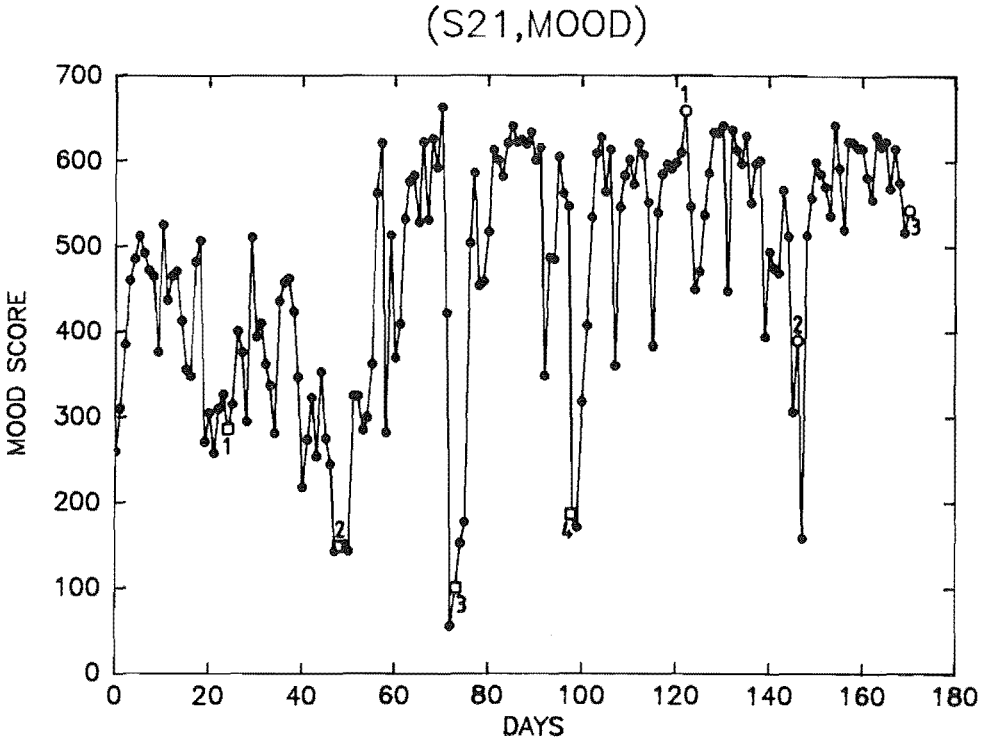

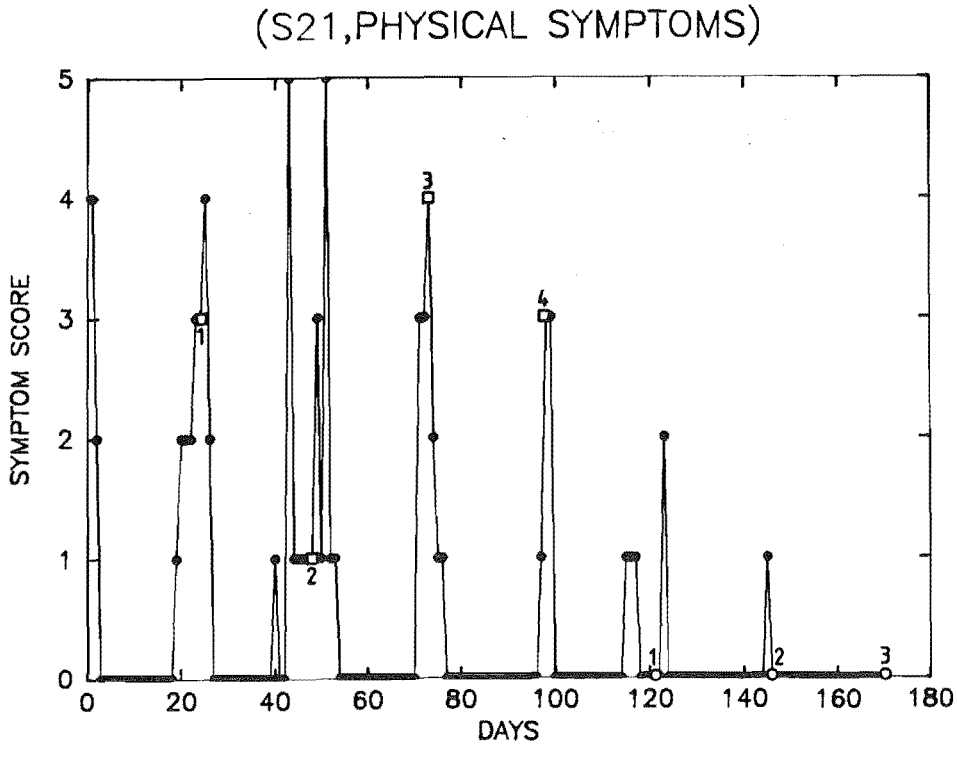

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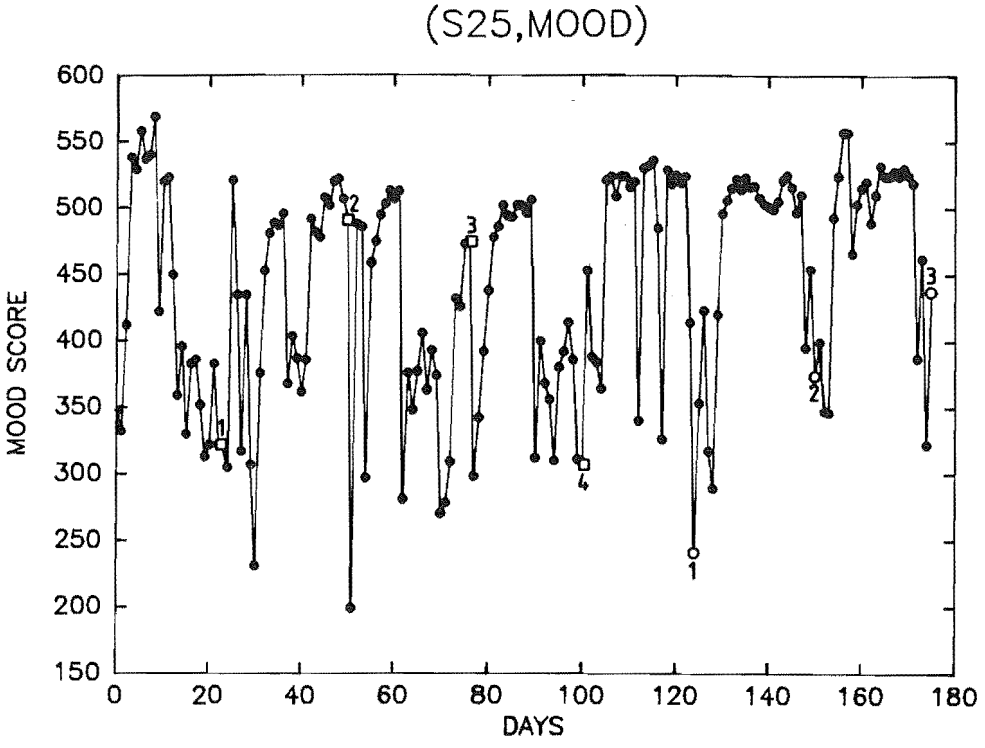

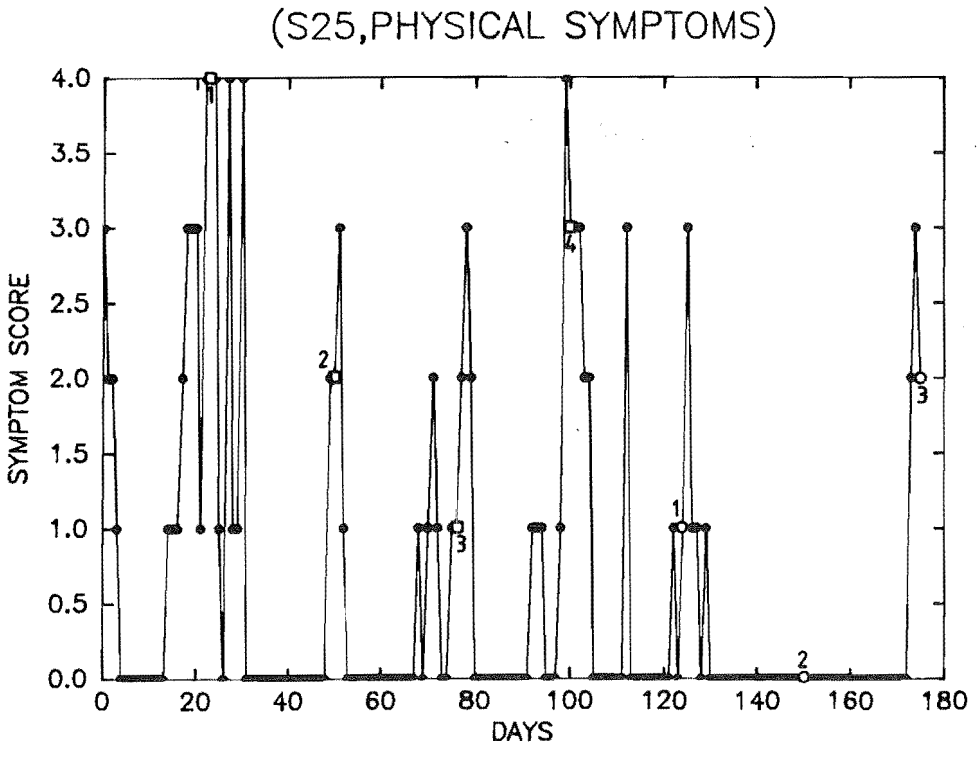

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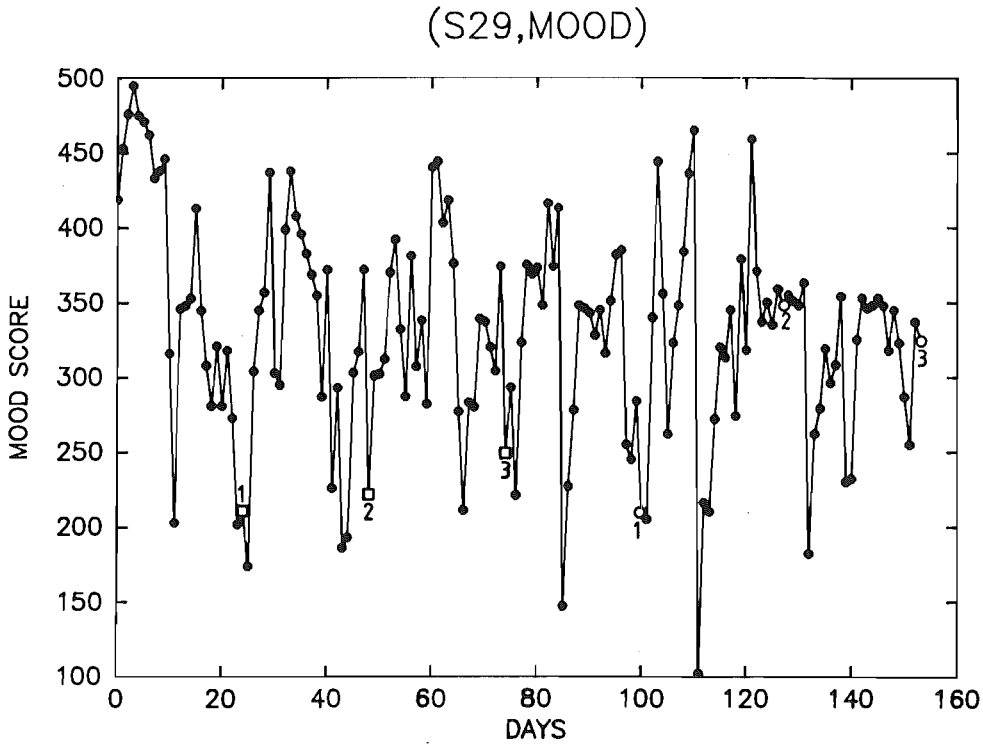

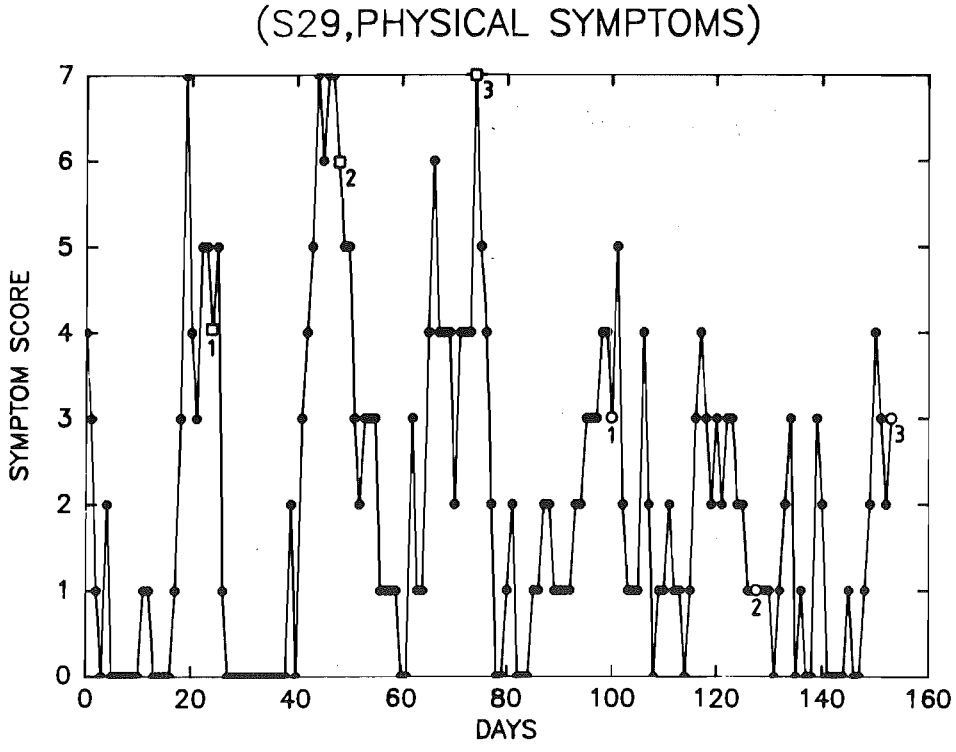

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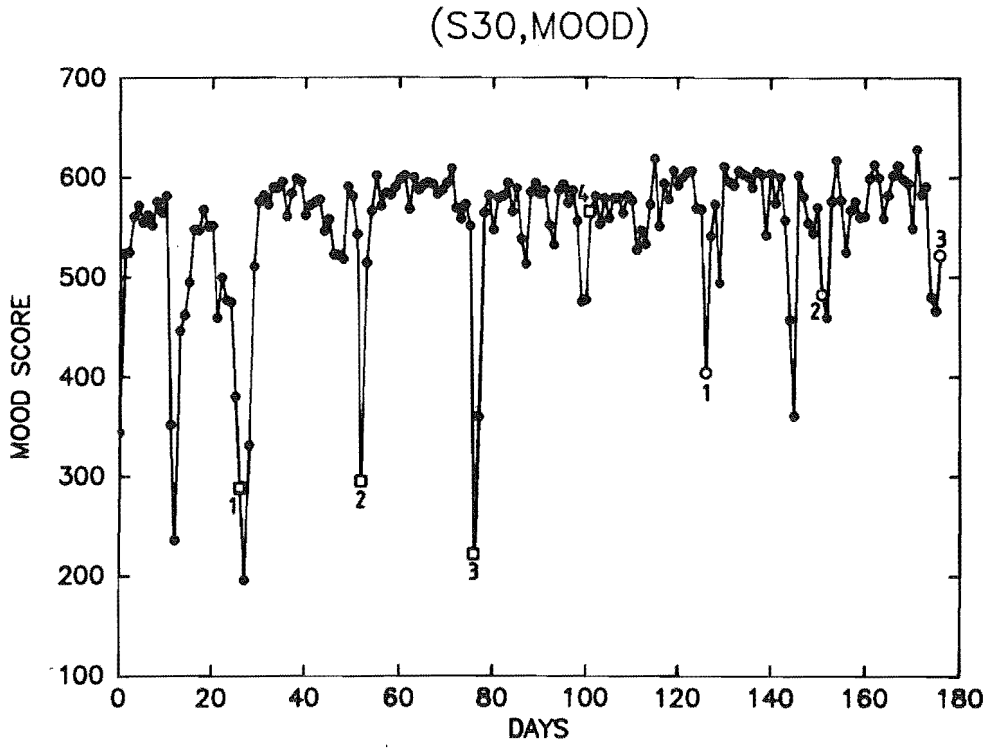

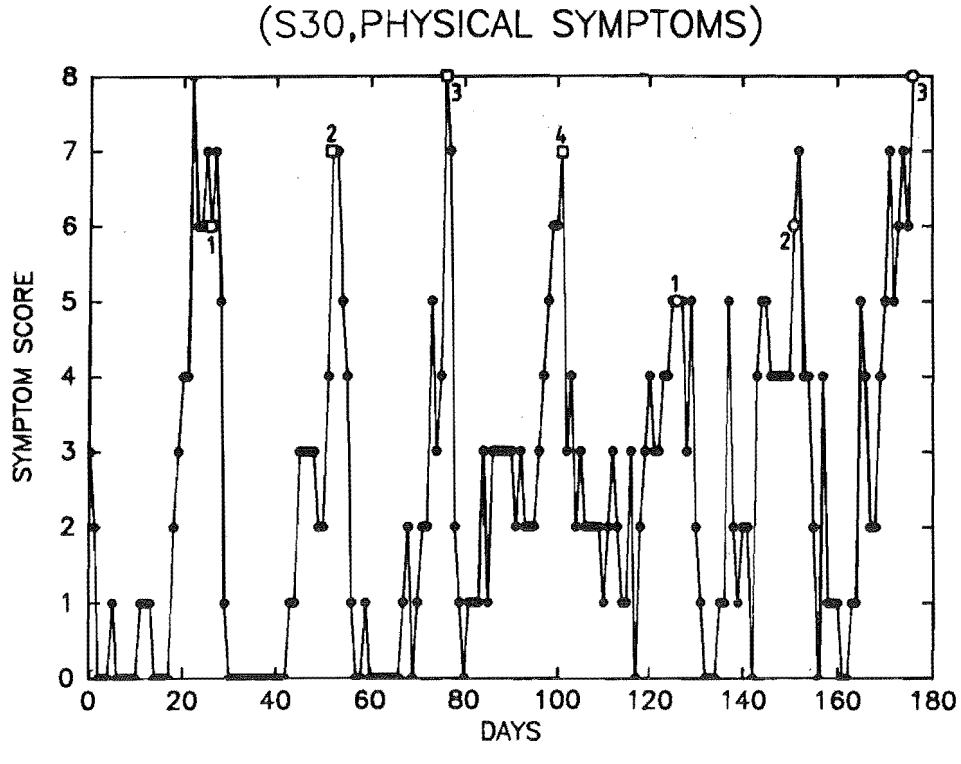

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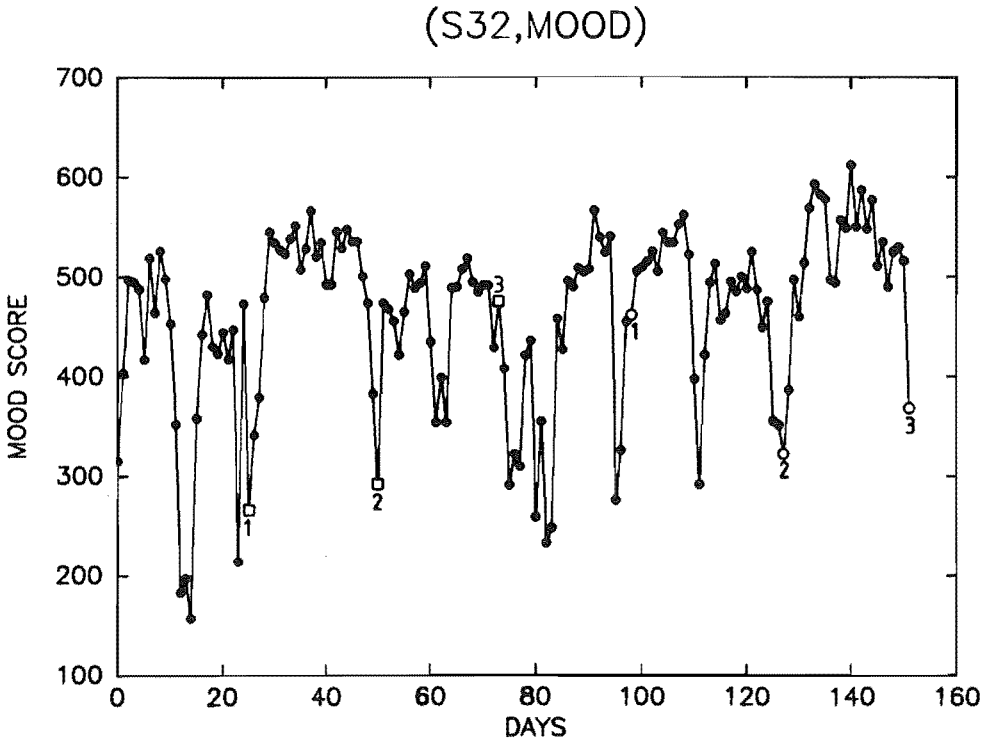

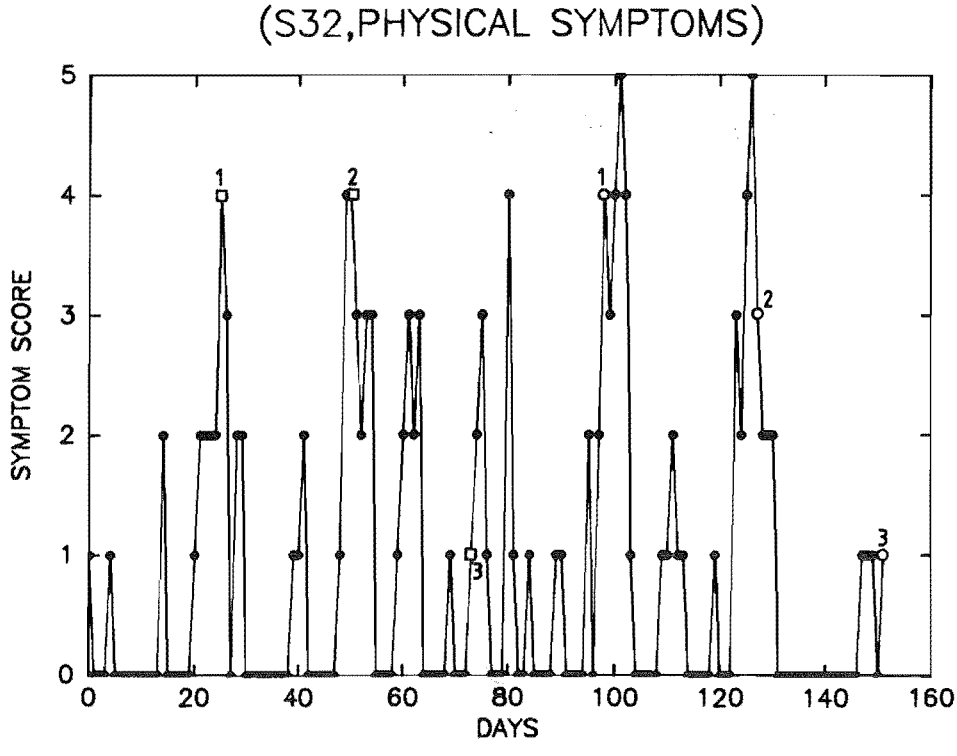

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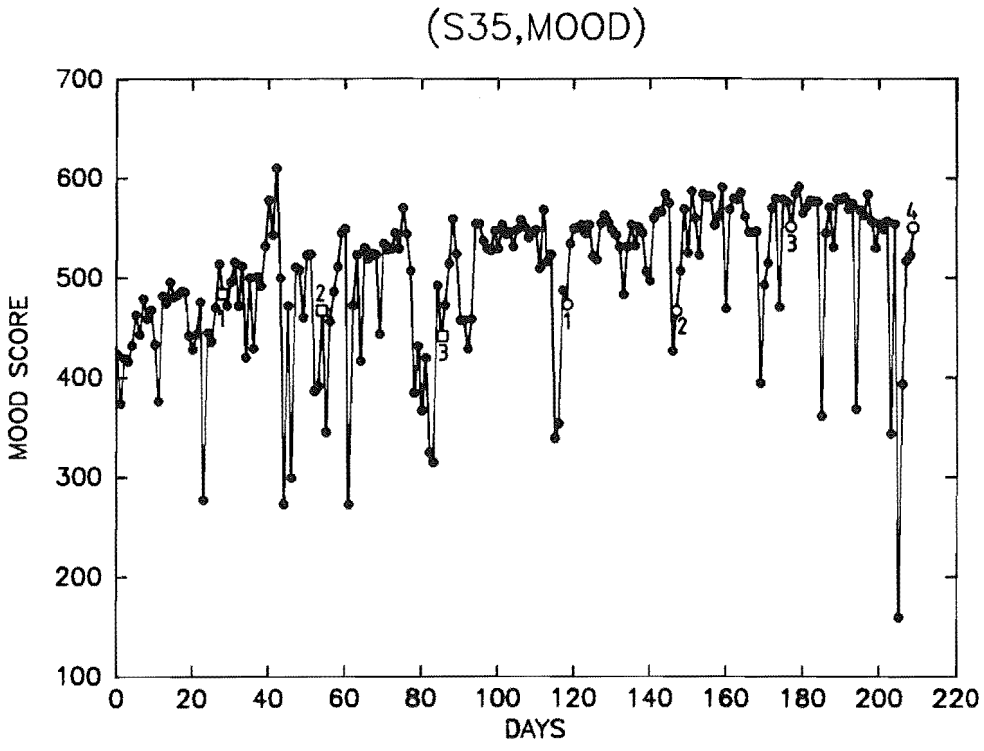
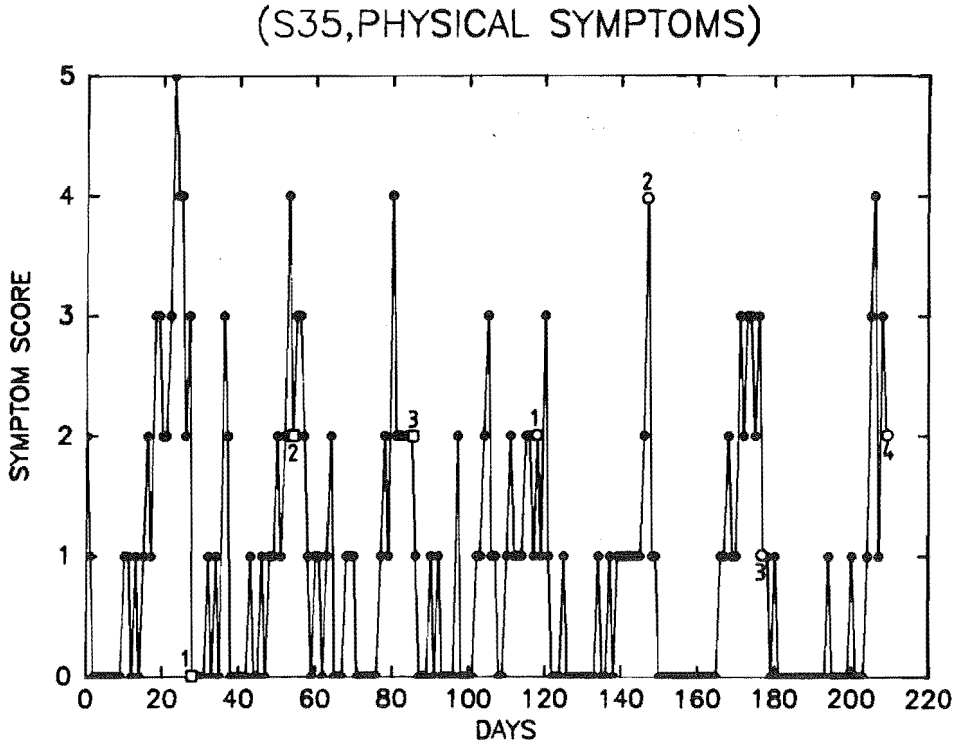
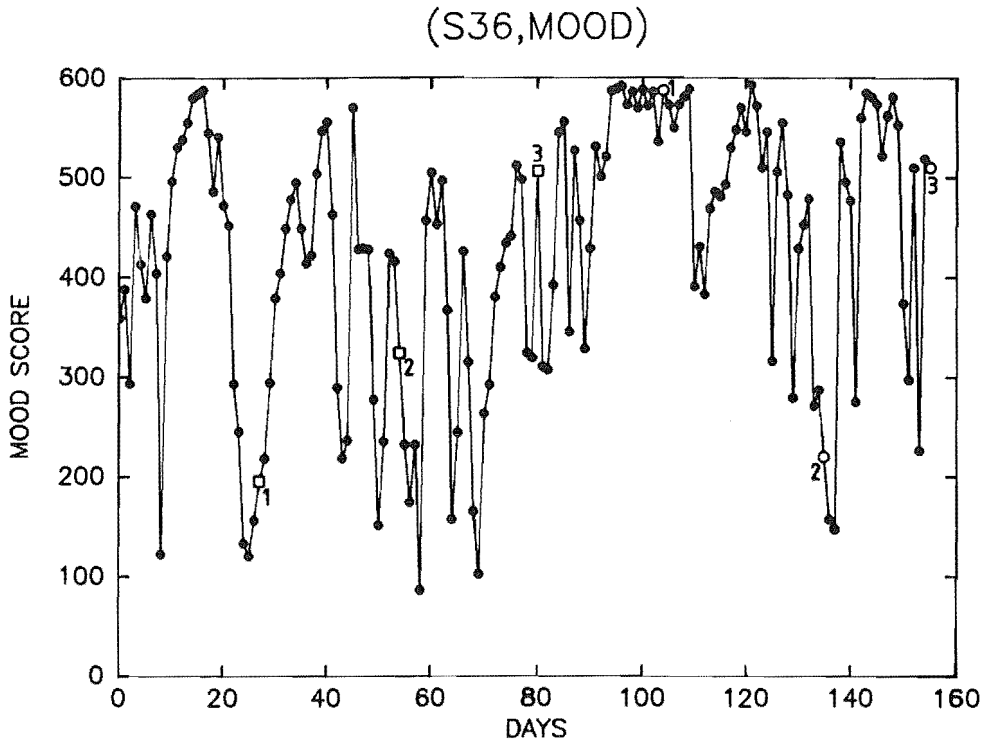


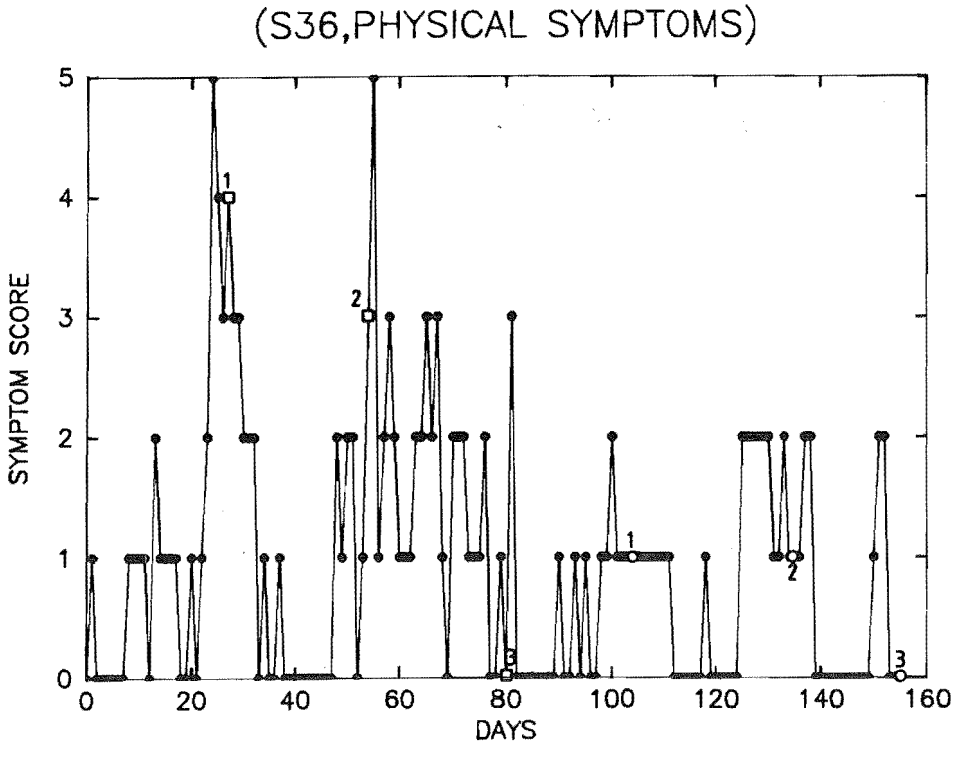


□= Control cycle 1 (etc)

○= Placebo cycle 1 (etc)

Appendix 5 continued: -

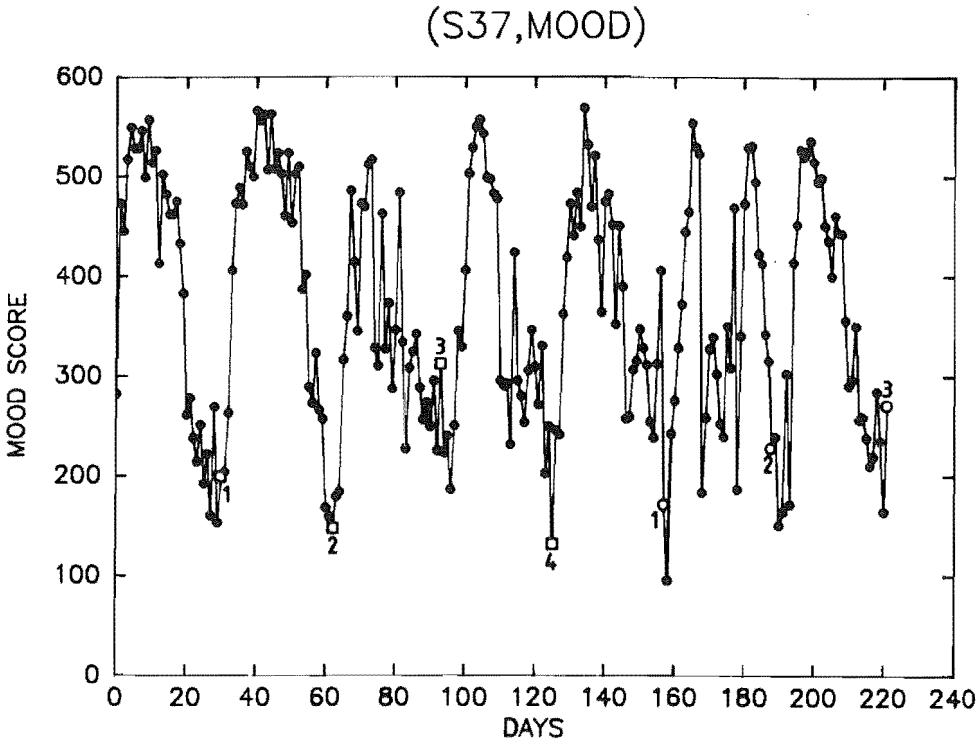


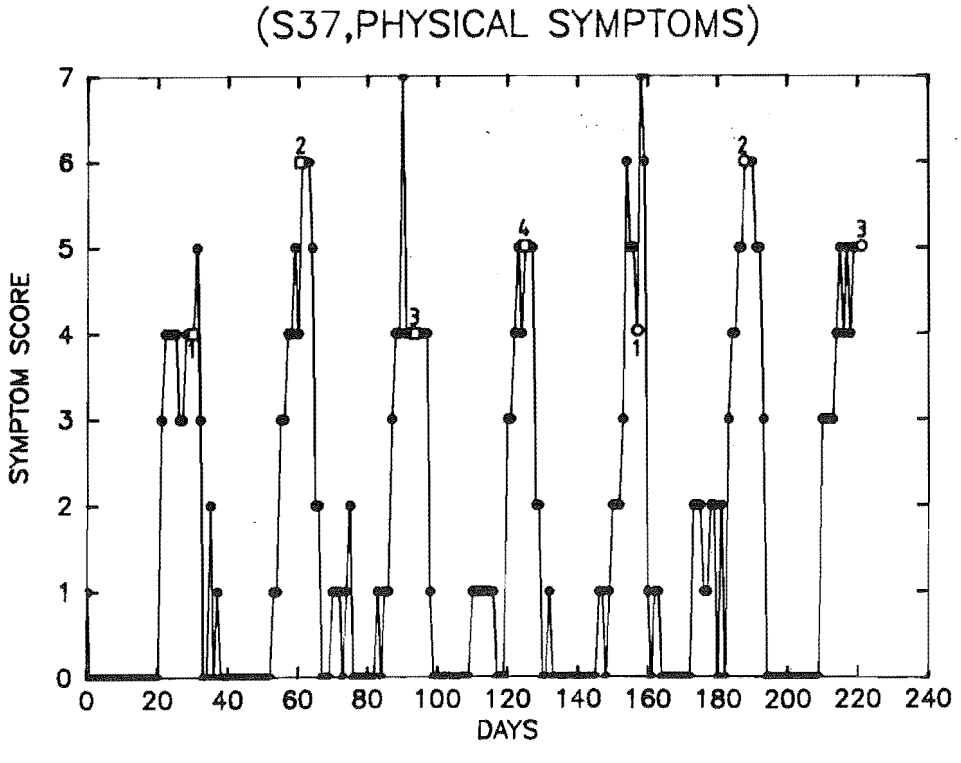


□= Control cycle 1 (etc)

○= Placebo cycle 1 (etc)

Appendix 5 continued: -

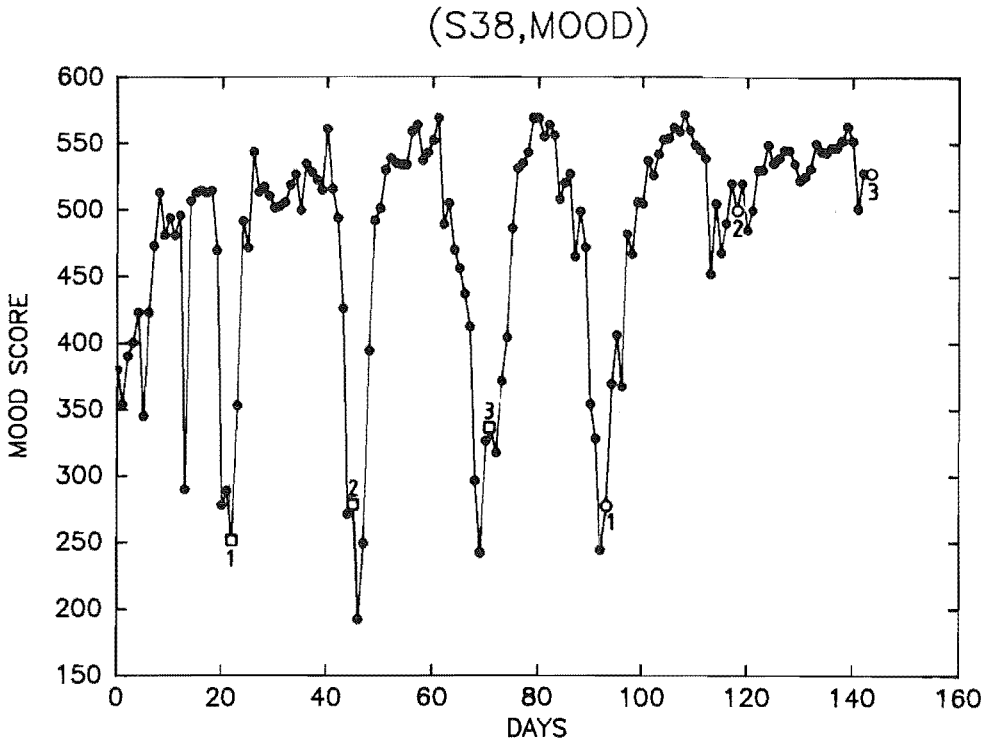


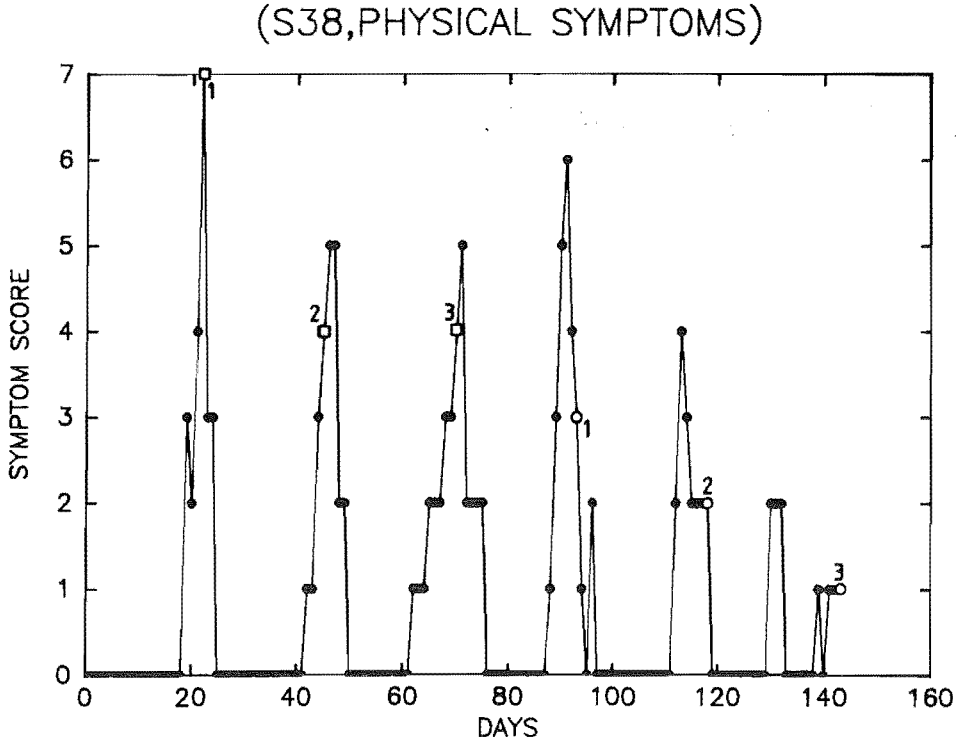


□= Control cycle 1 (etc)

○= Placebo cycle 1 (etc)

Appendix 5 continued: -

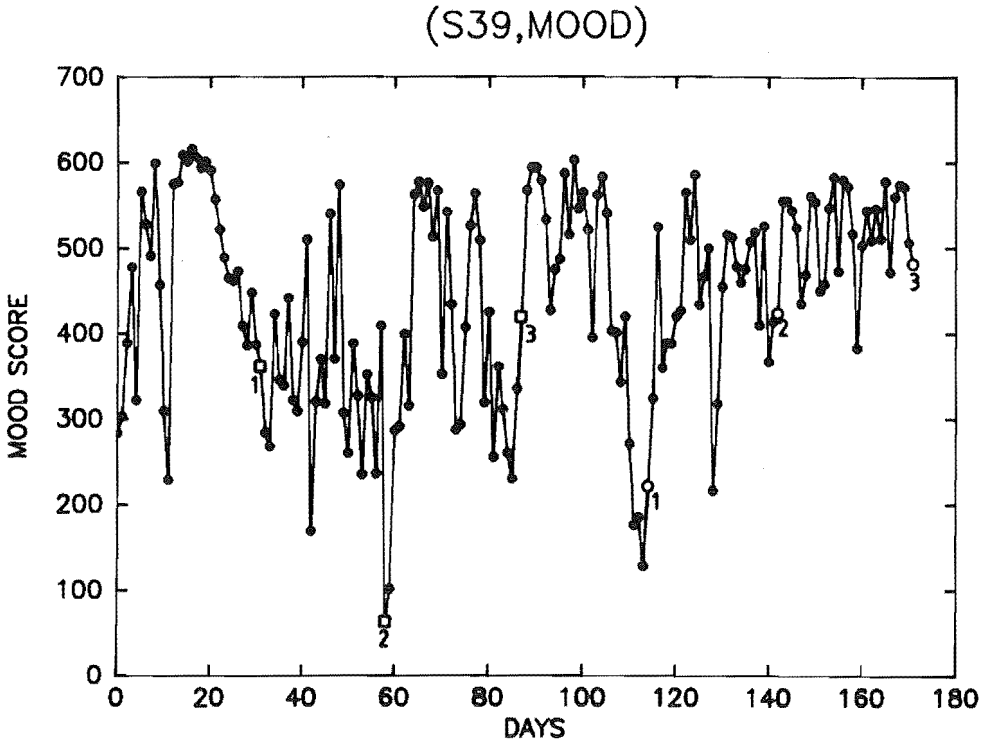


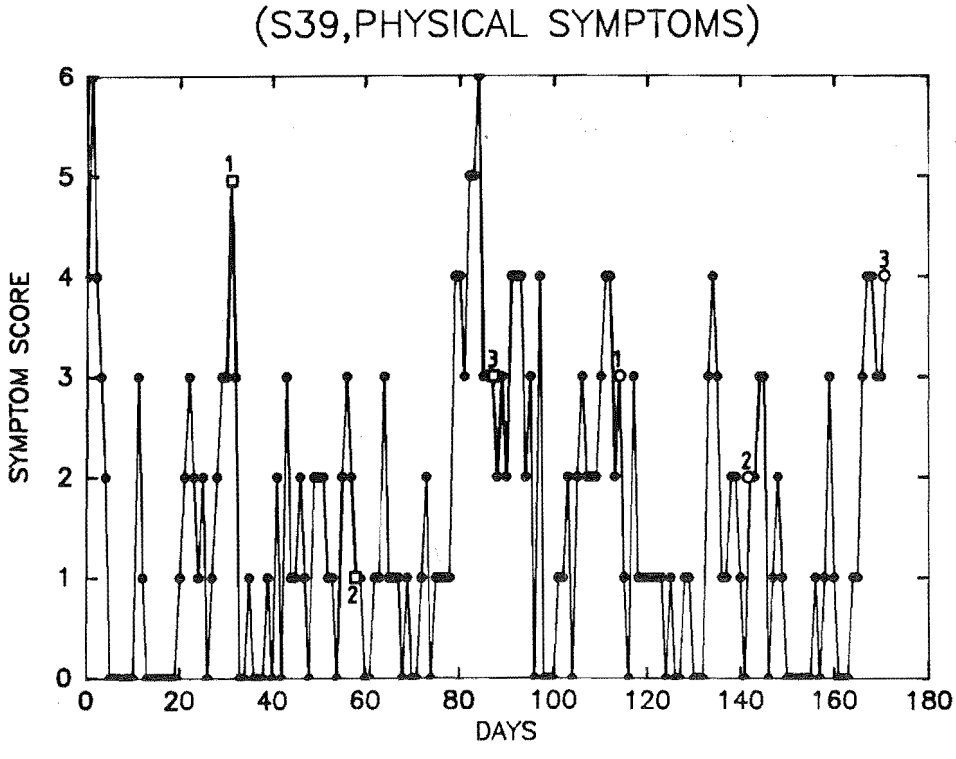


□ = Control cycle 1 (etc)

○ = Placebo cycle 1 (etc)

Appendix 5 continued: -

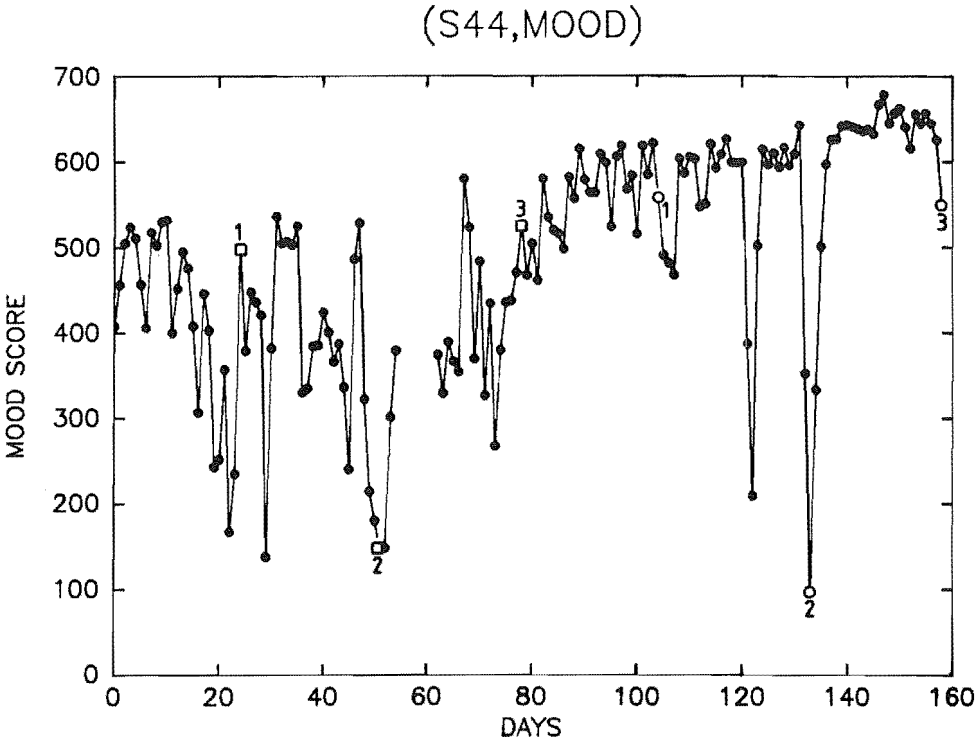


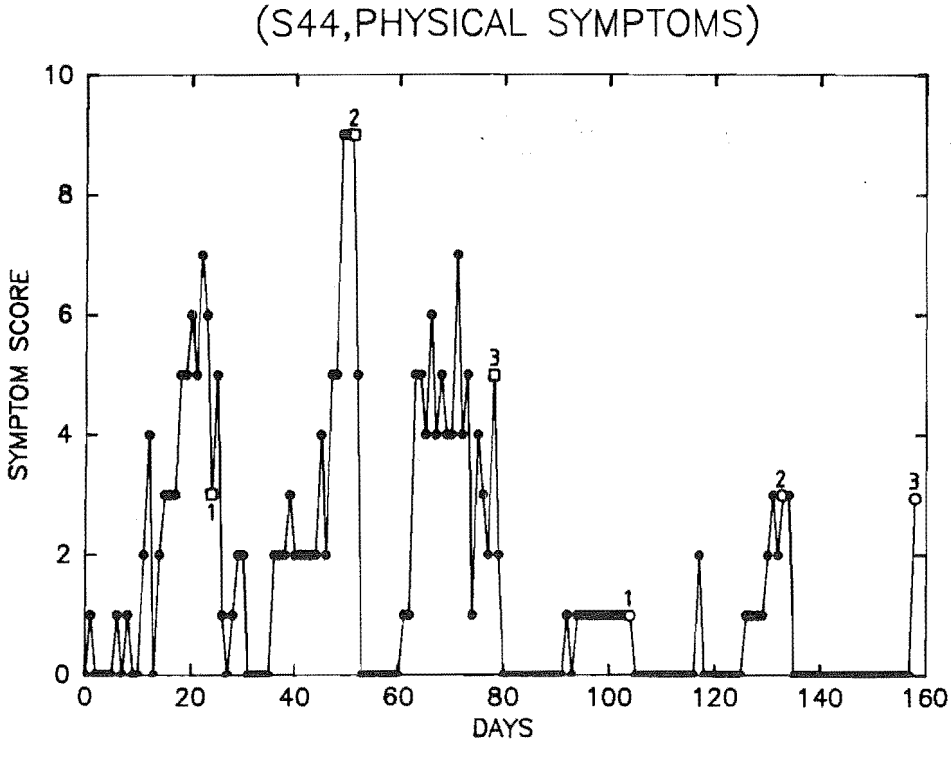


□ = Control cycle 1 (etc)

○ = Placebo cycle 1 (etc)

Appendix 5 continued: -

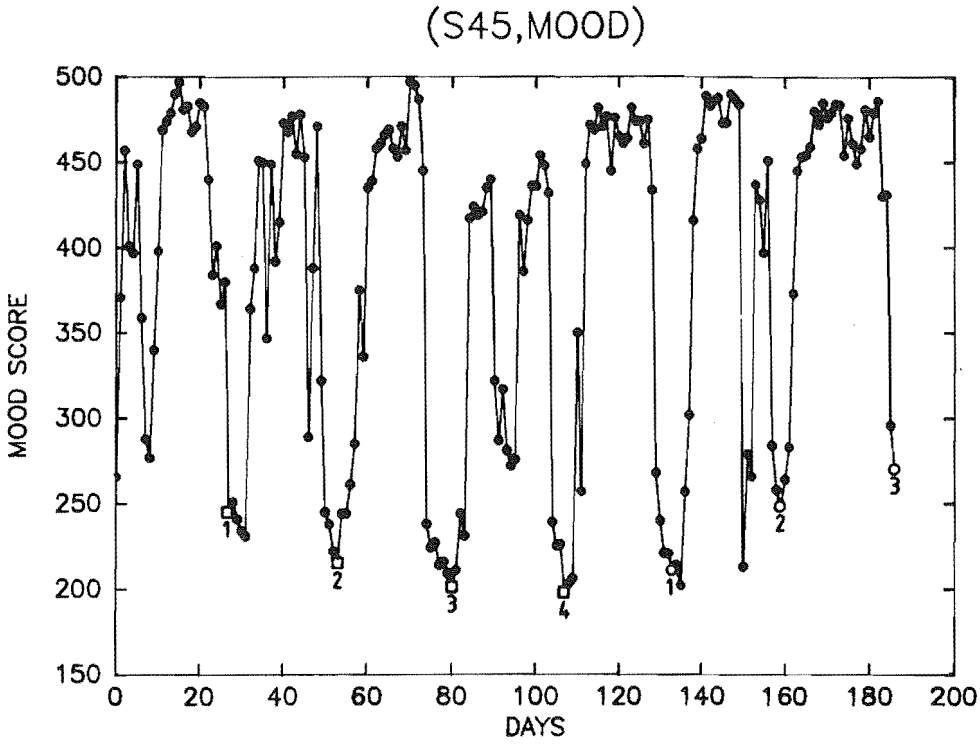


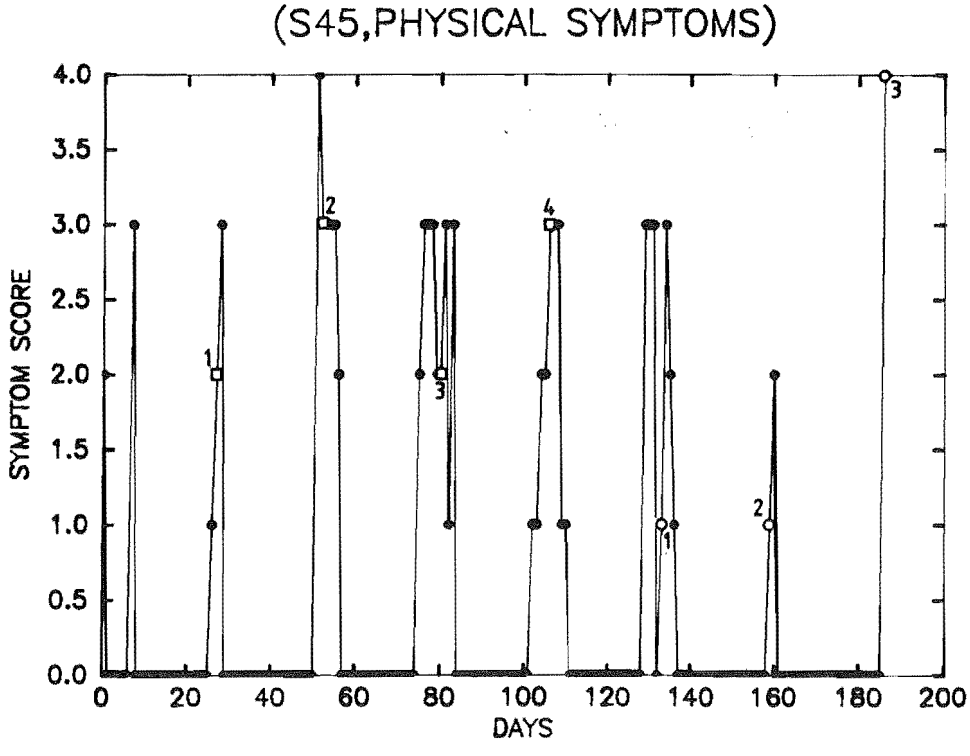


□= Control cycle 1 (etc)

○= Placebo cycle 1 (etc)

Appendix 5 continued: -

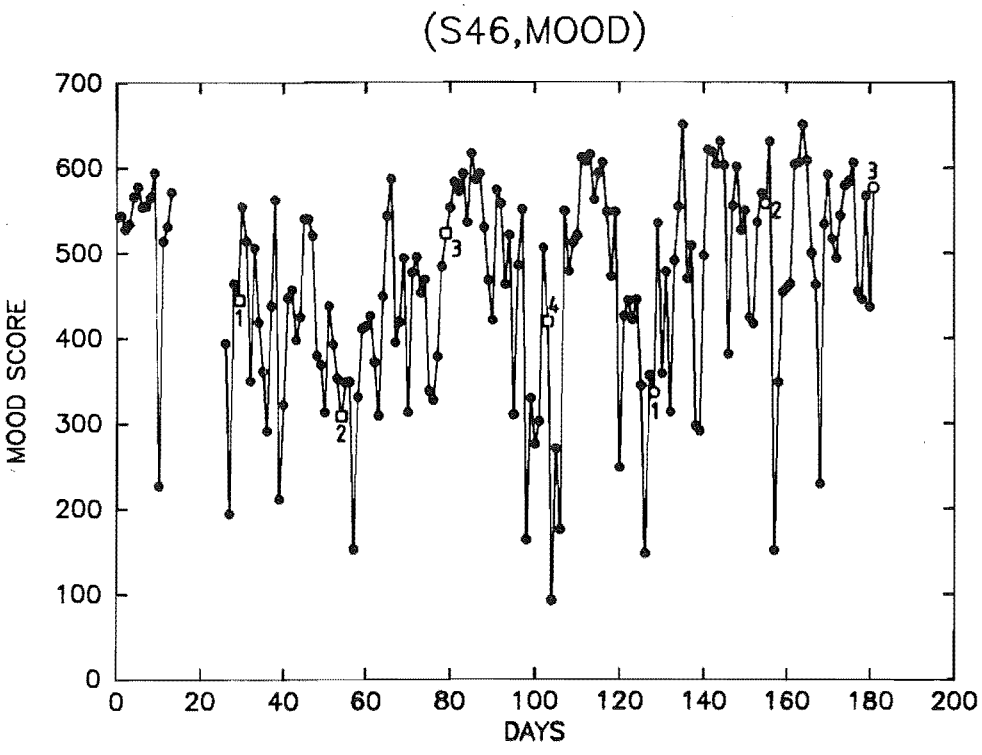


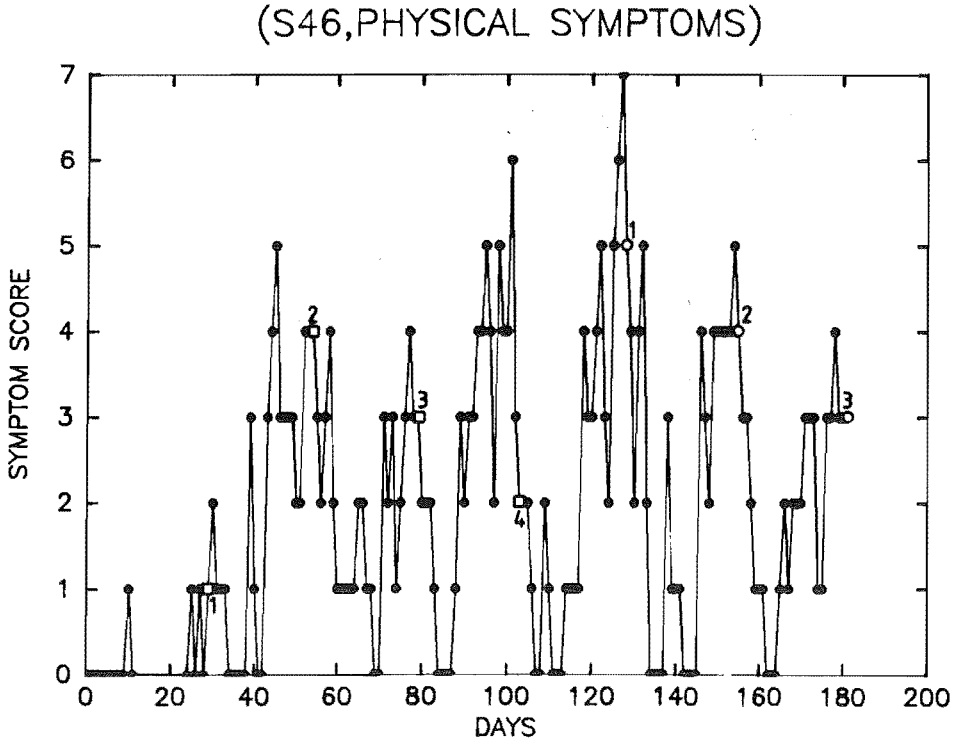


□= Control cycle 1 (etc)

○= Placebo cycle 1 (etc)

Appendix 5 continued: -

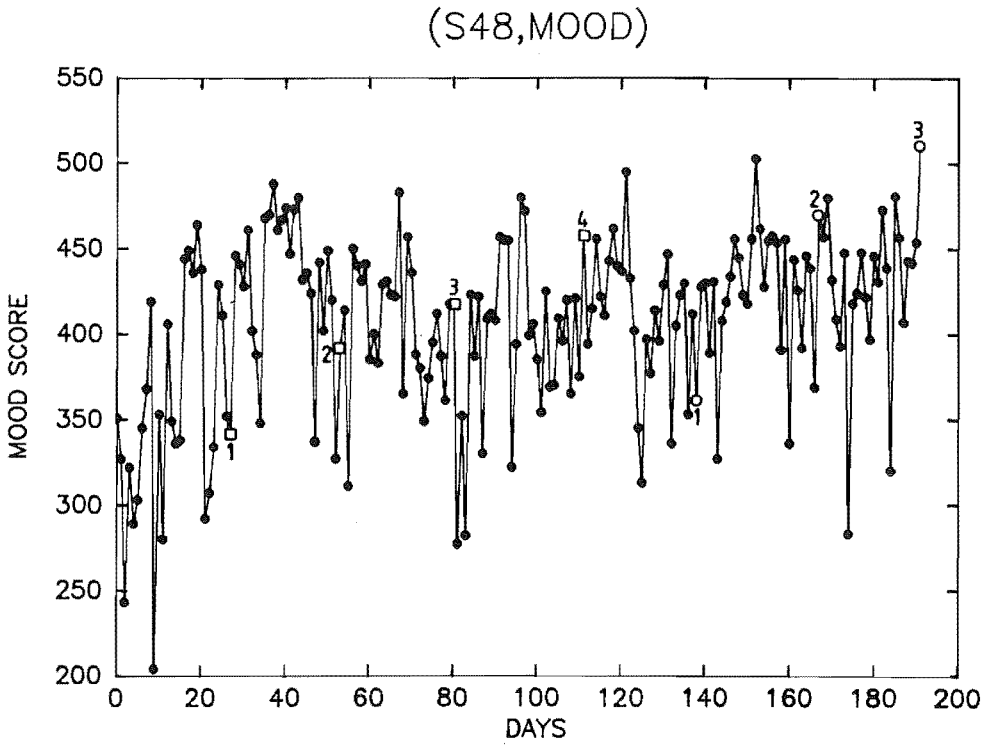


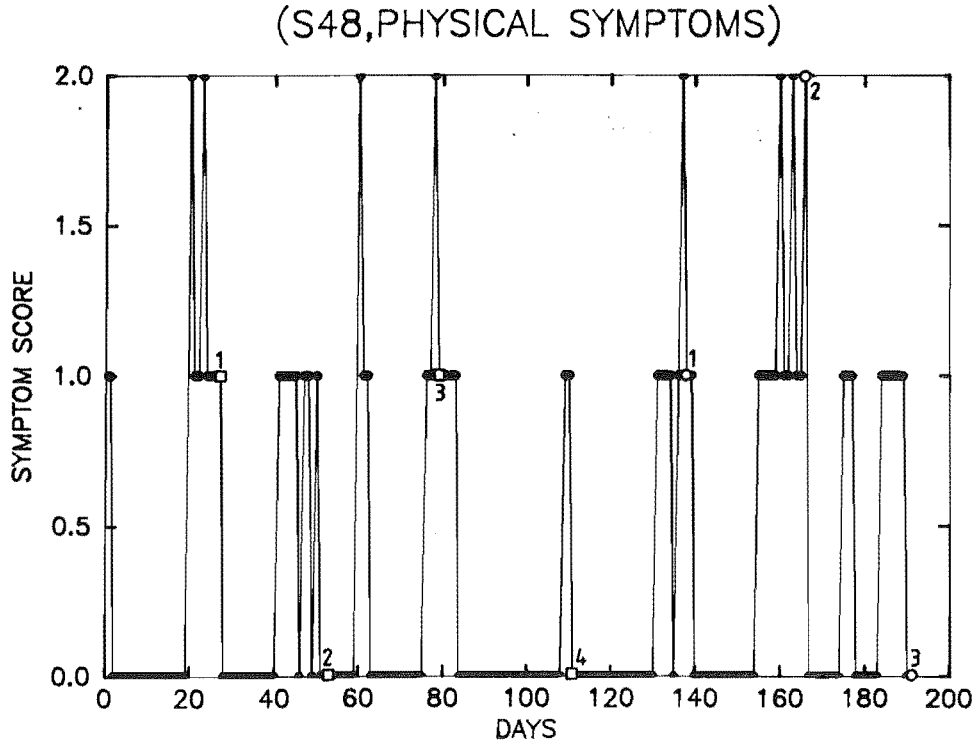


□= Control cycle 1 (etc)

○= Placebo cycle 1 (etc)

Appendix 5 continued: -

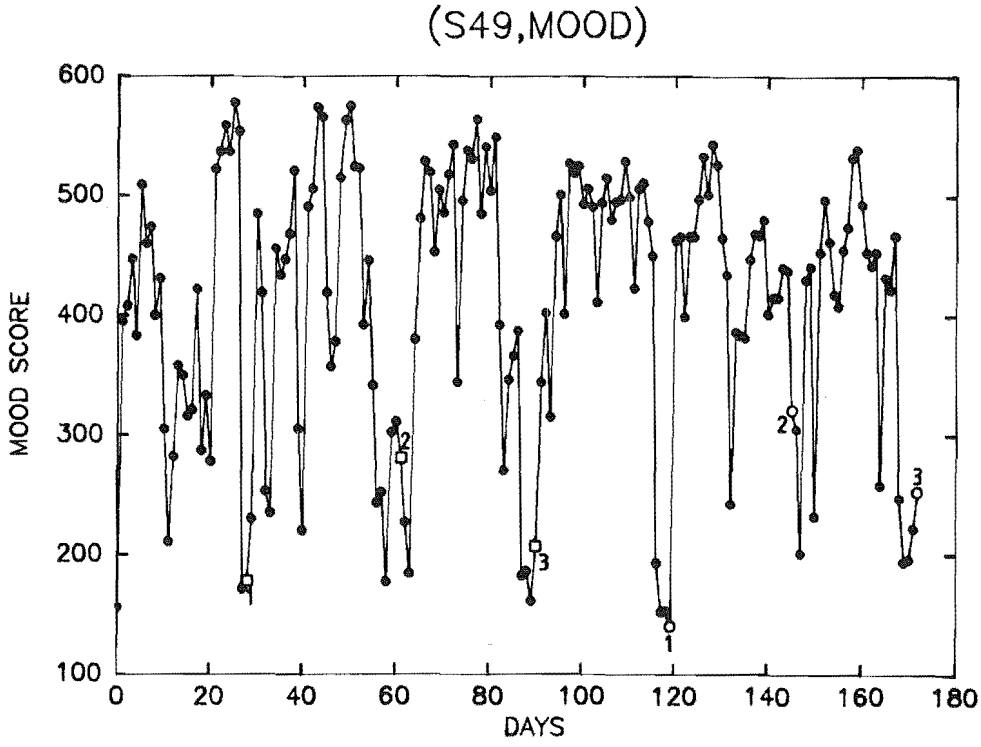


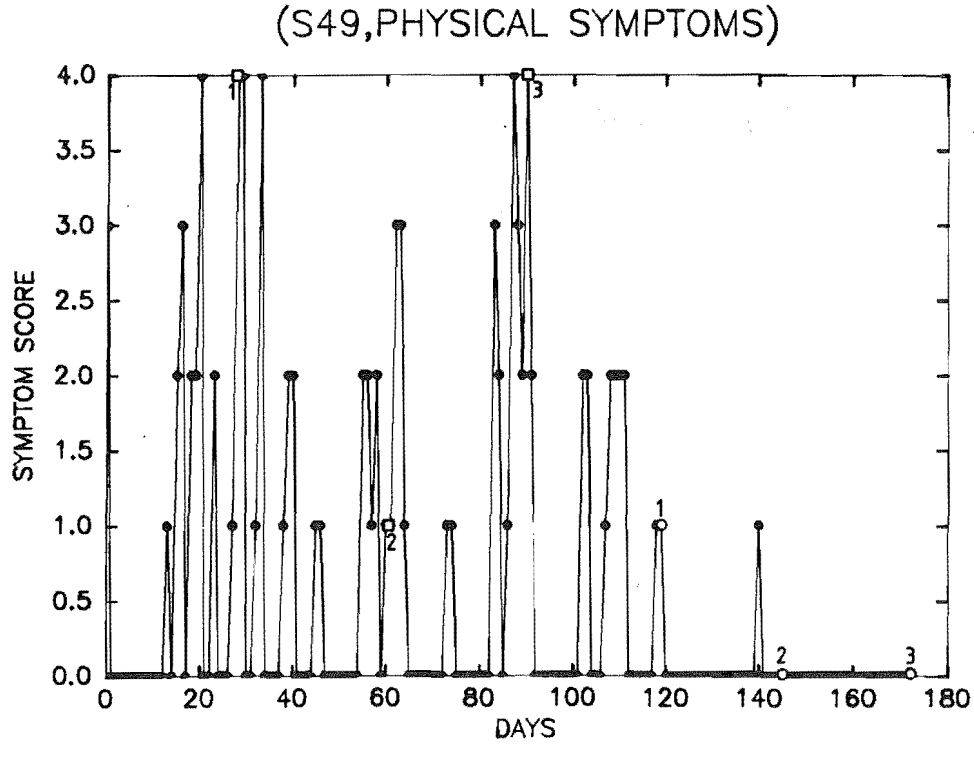


□ = Control cycle 1 (etc)

○ = Placebo cycle 1 (etc)

Appendix 5 continued: -

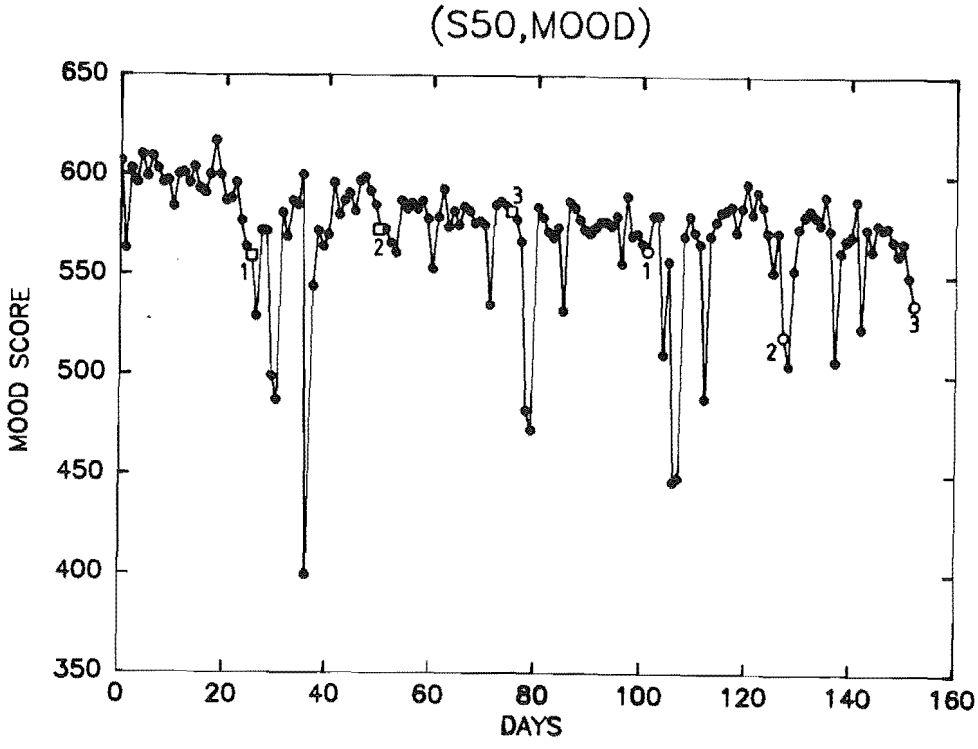


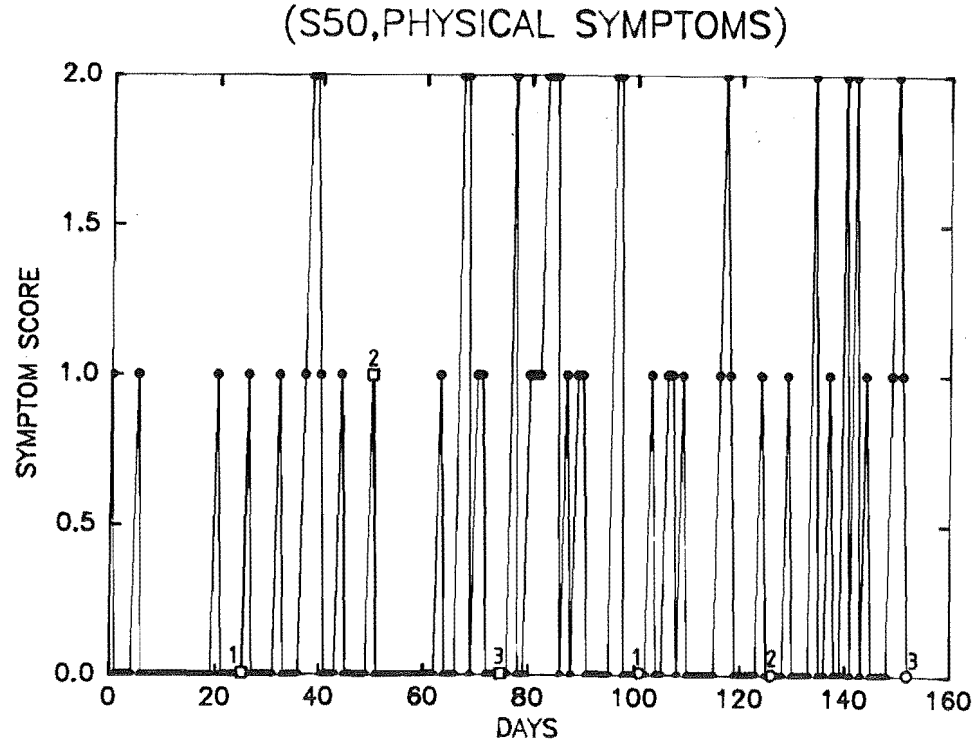


□= Control cycle 1 (etc)

○= Placebo cycle 1 (etc)

Appendix 5 continued: -





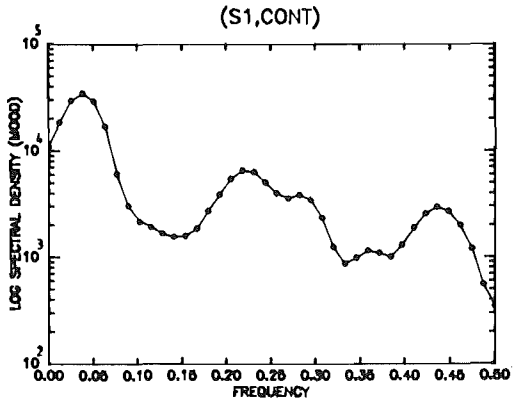
□ = Control cycle 1 (etc)

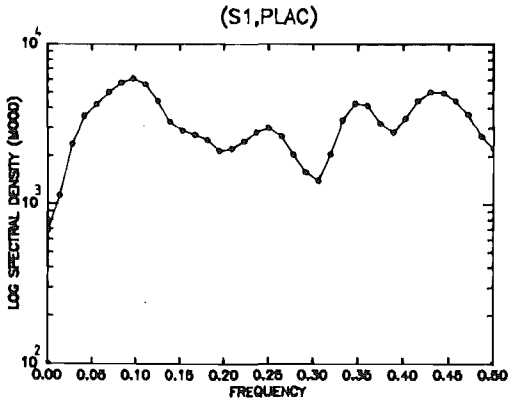
○ = Placebo cycle 1 (etc)

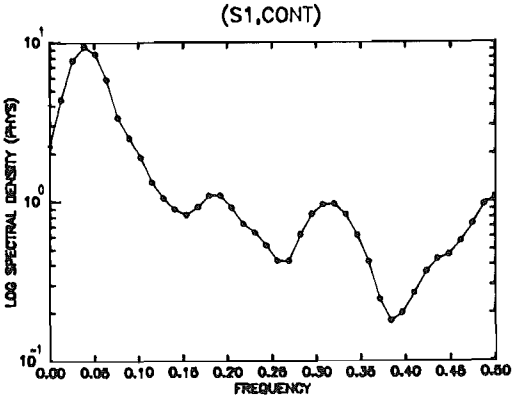
Appendix 6

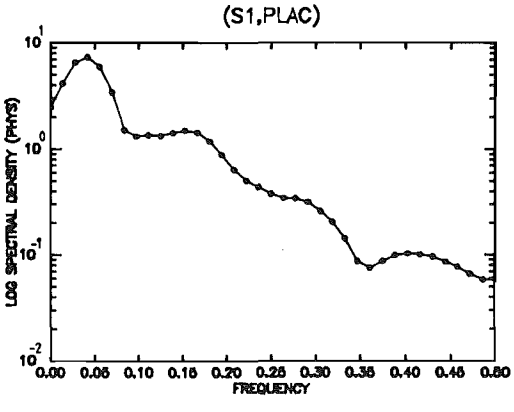
Mood and Physical Symptom Log Spectral Density, Coherence and Phase for Control and Placebo Cycles for each Subject

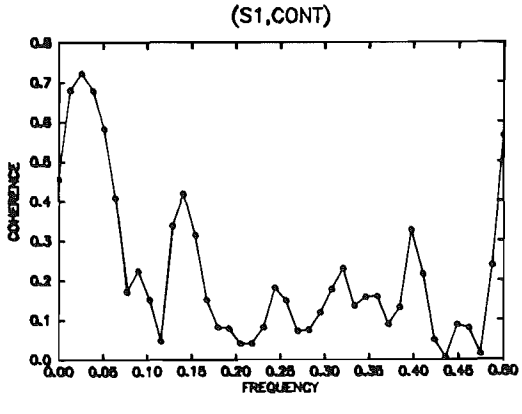
Appendix 6 continued: -

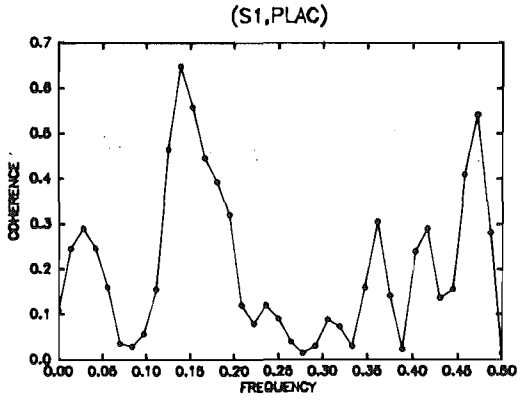


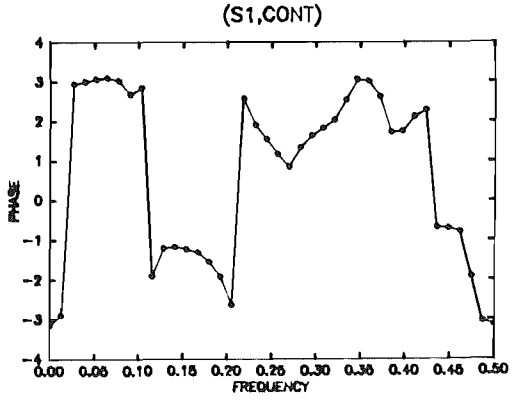


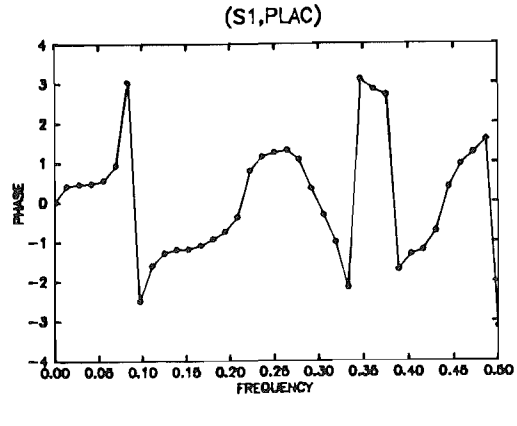












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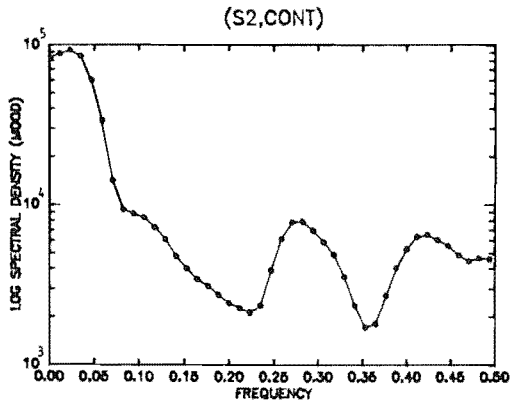

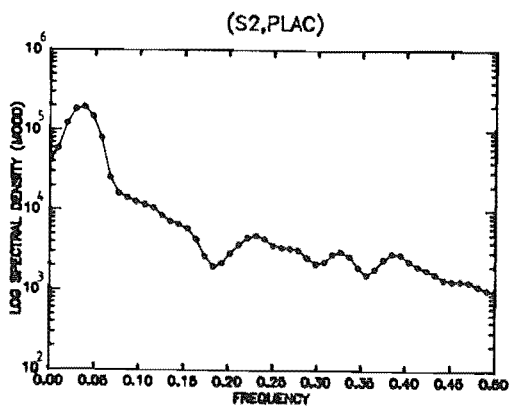

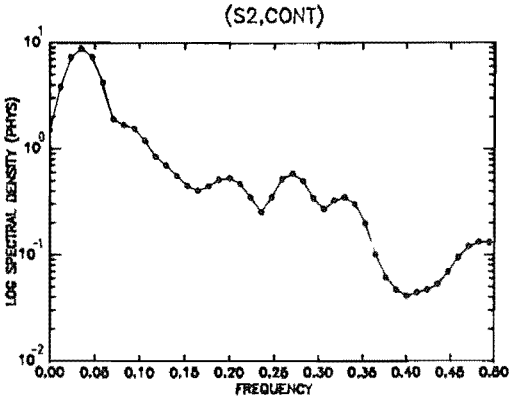

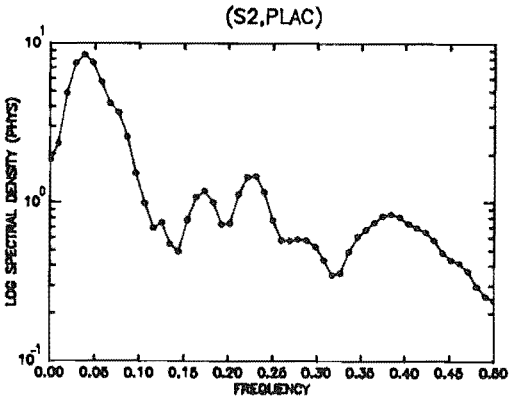

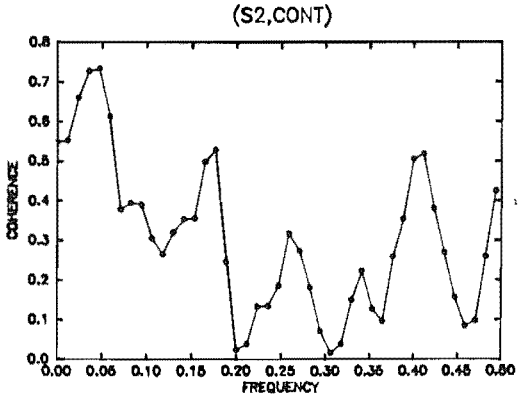

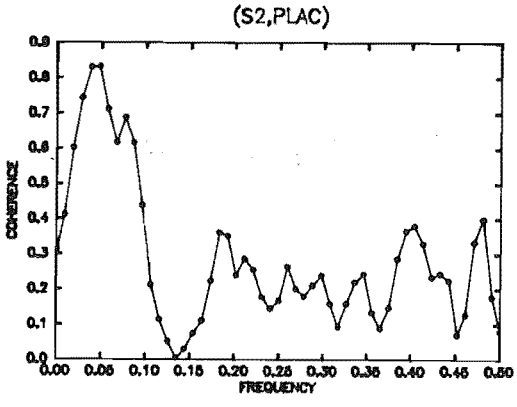

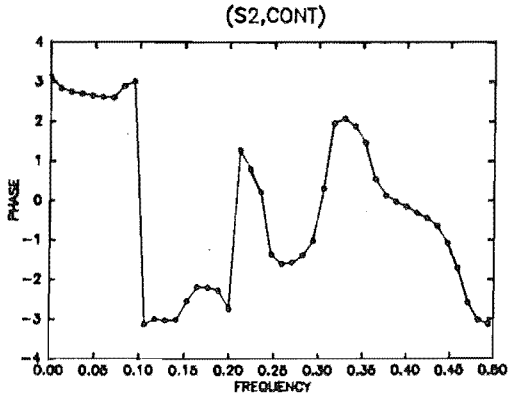

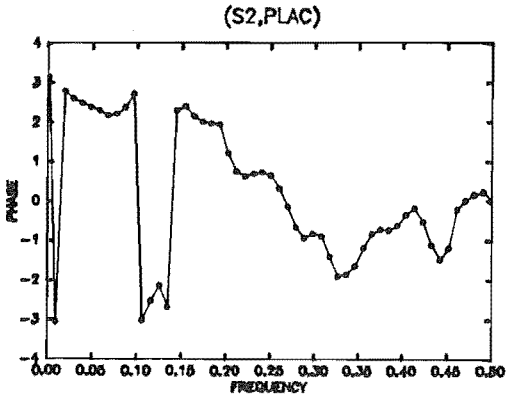

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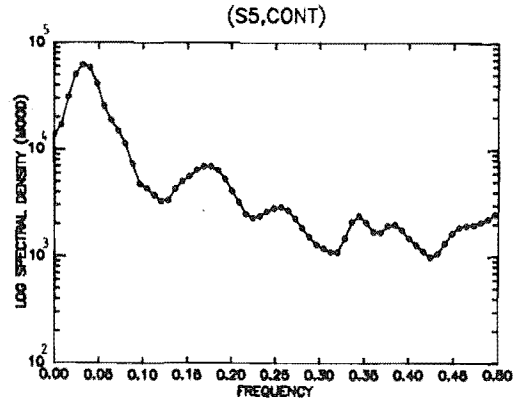

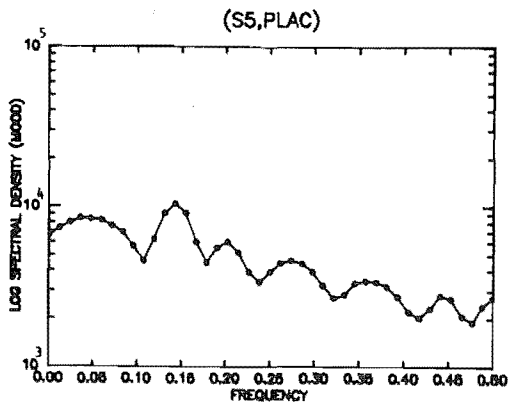

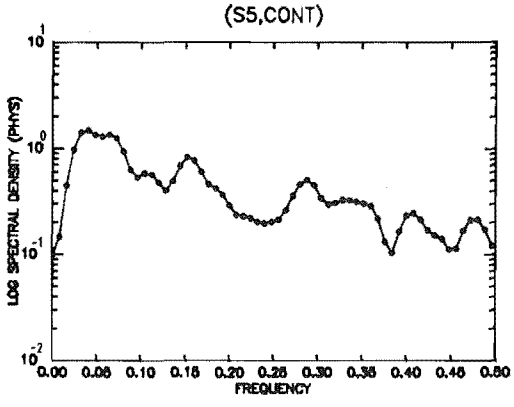

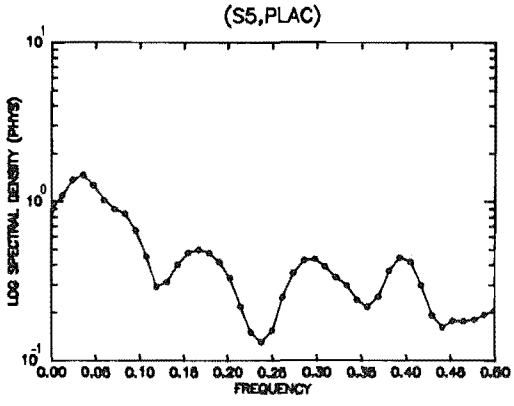

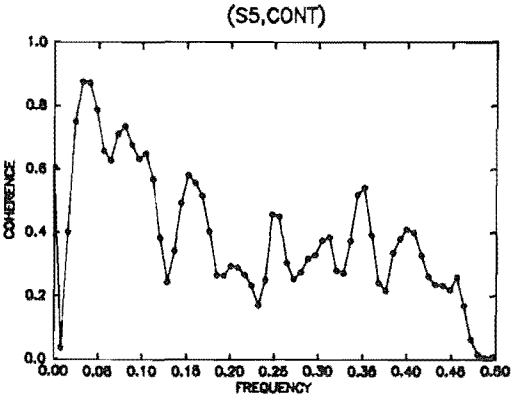

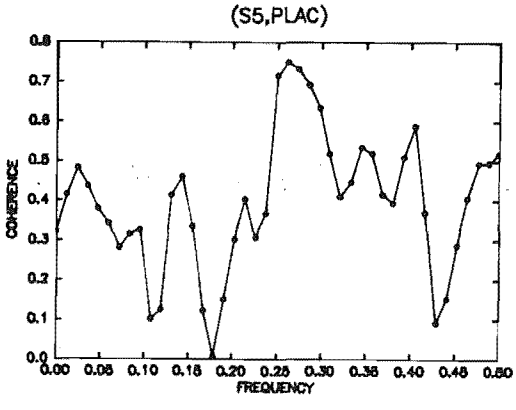

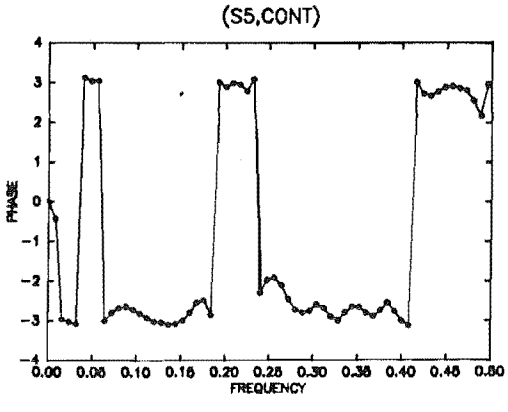

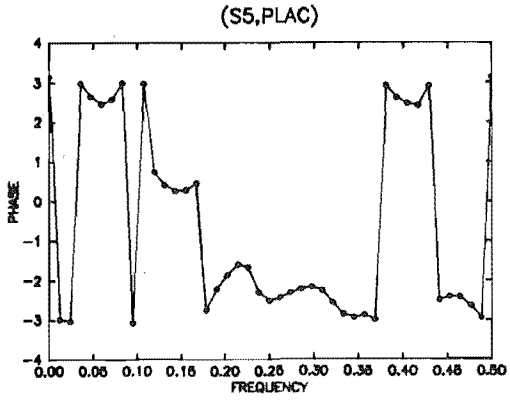

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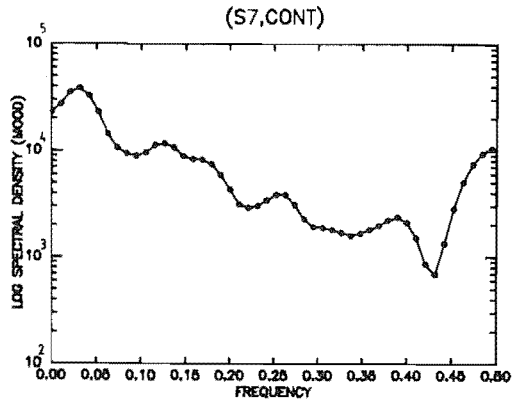

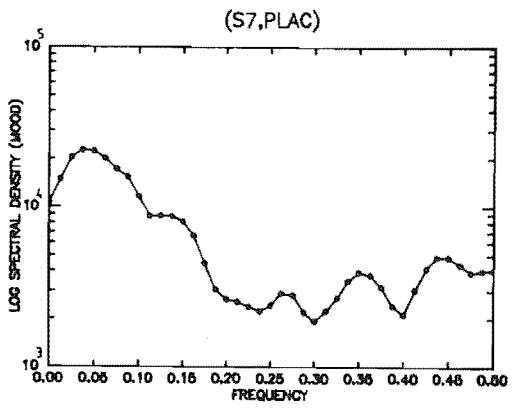

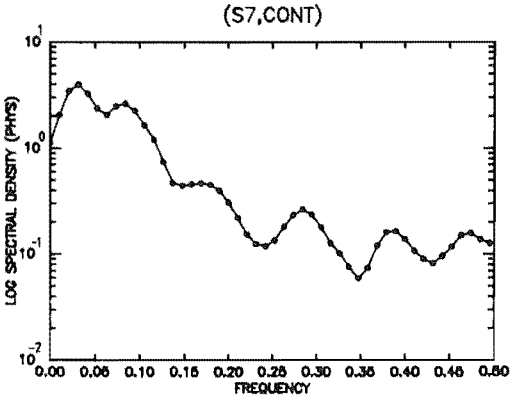

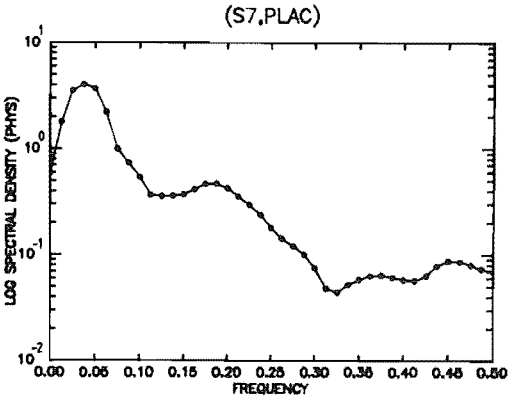

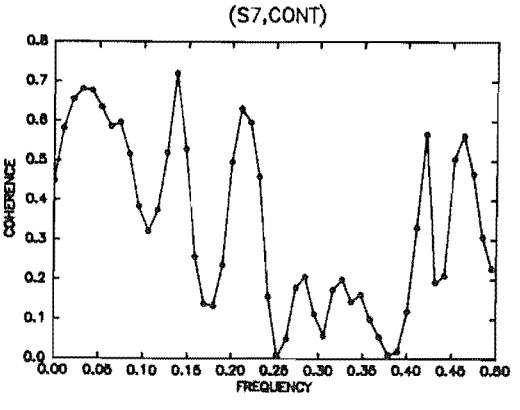

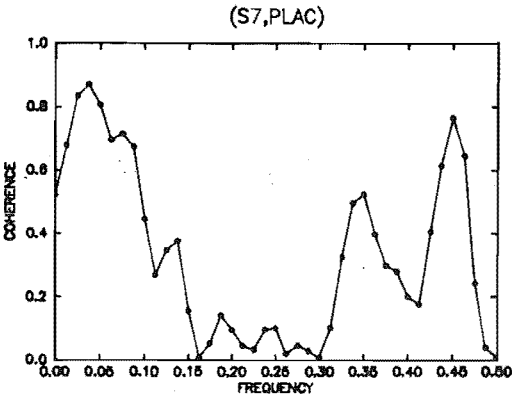

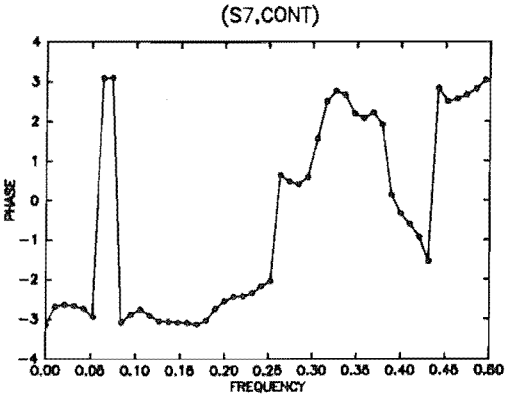

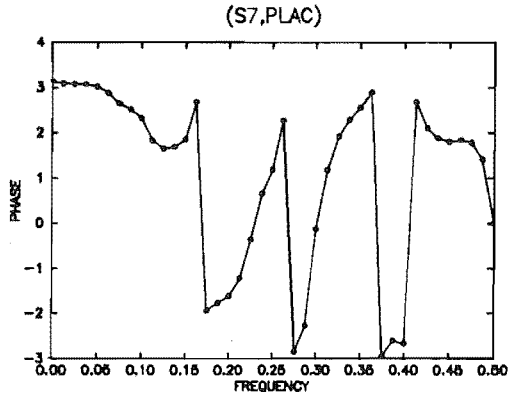

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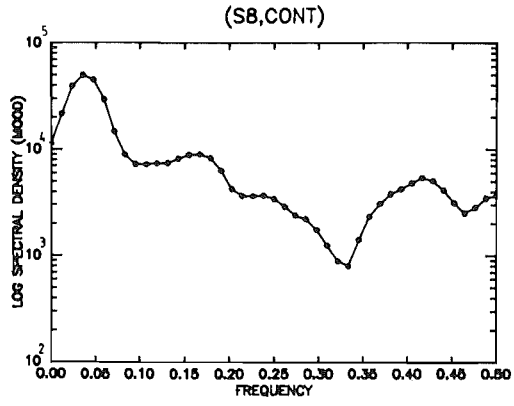

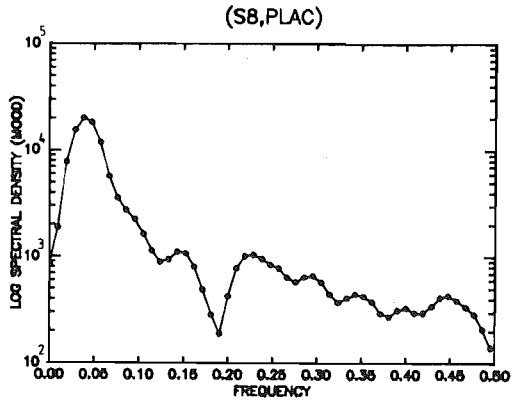

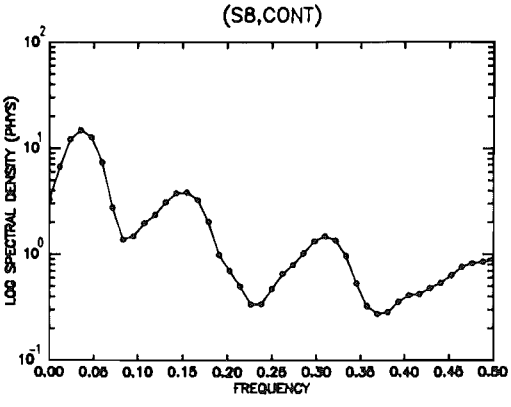

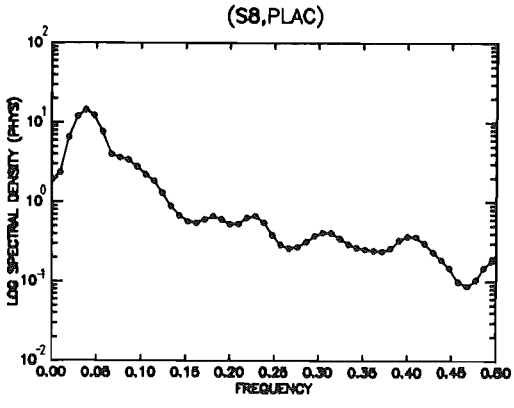

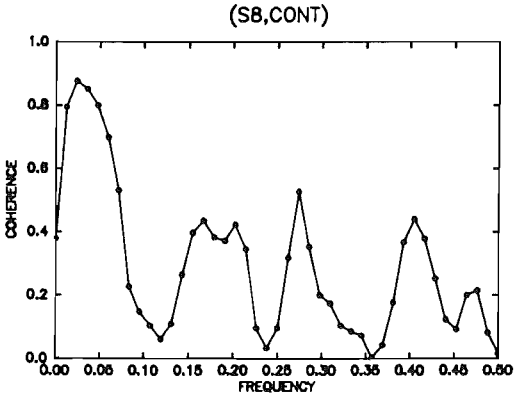

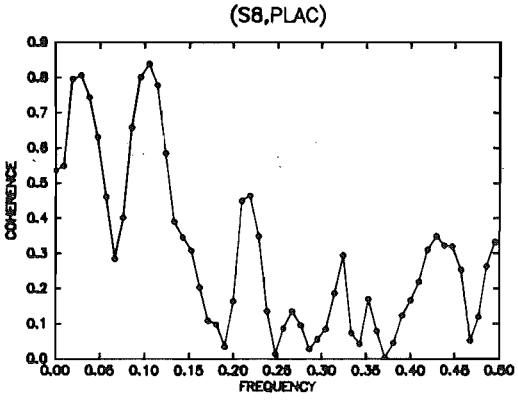

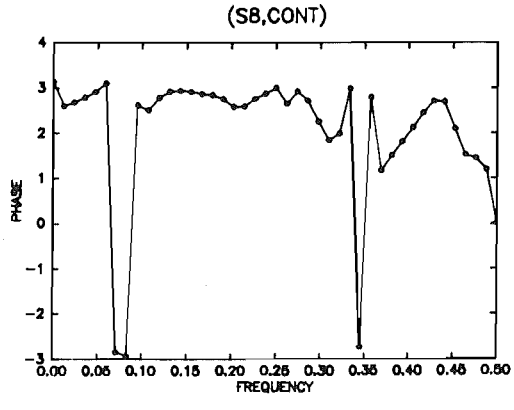

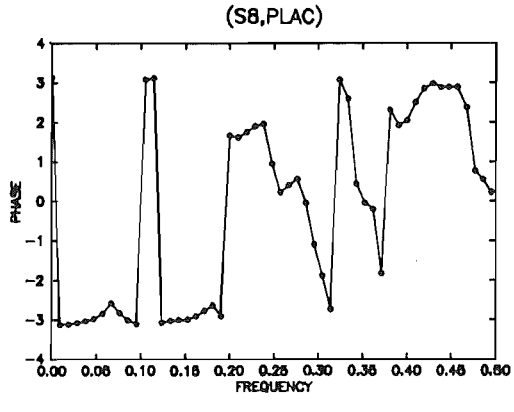

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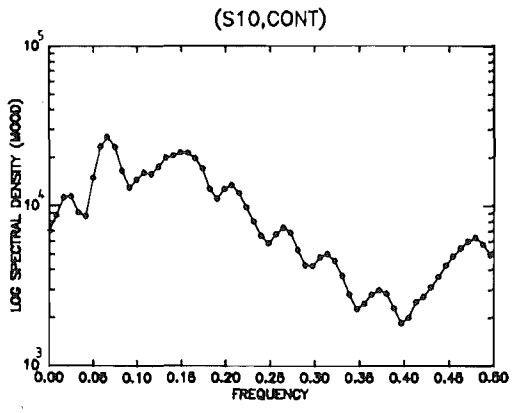

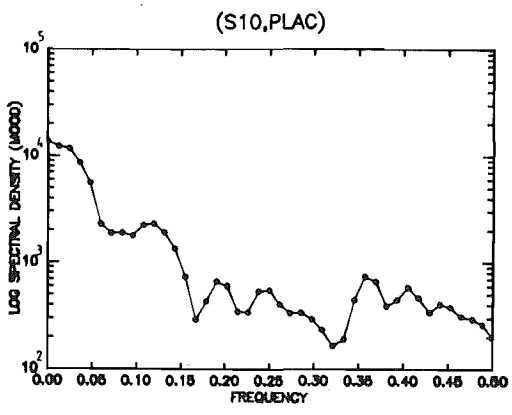

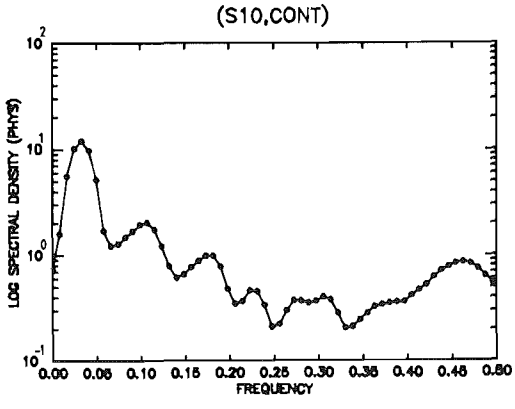

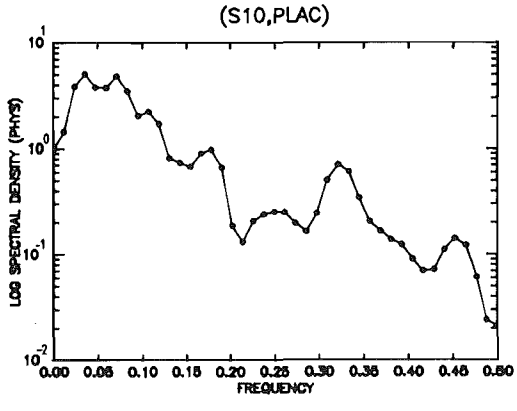

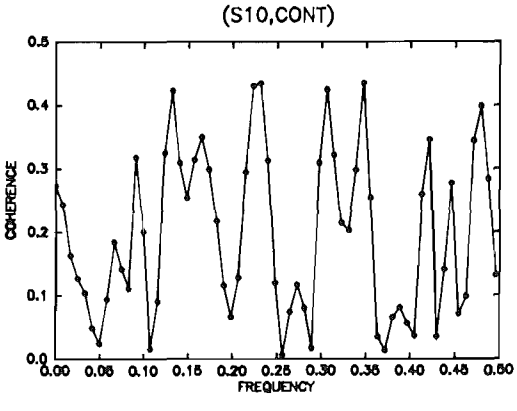

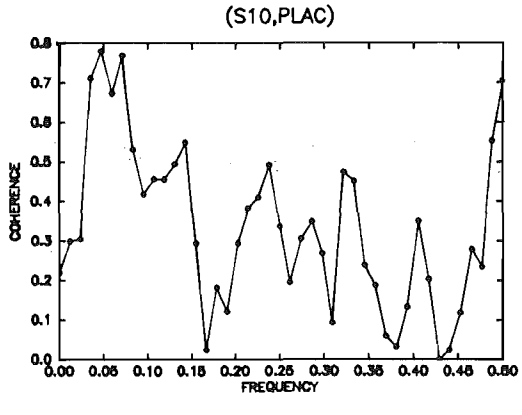

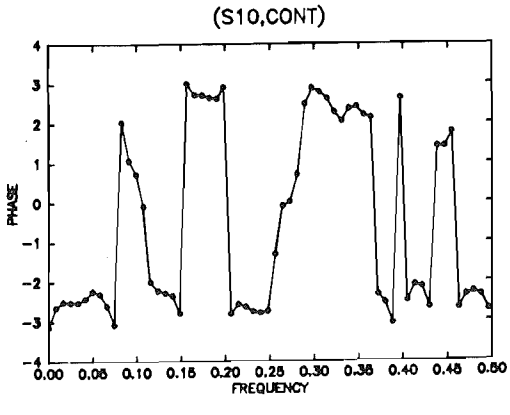

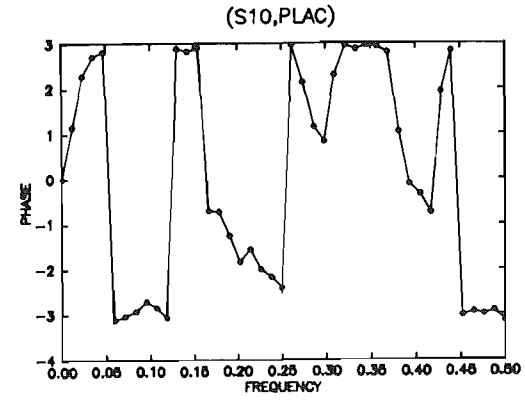

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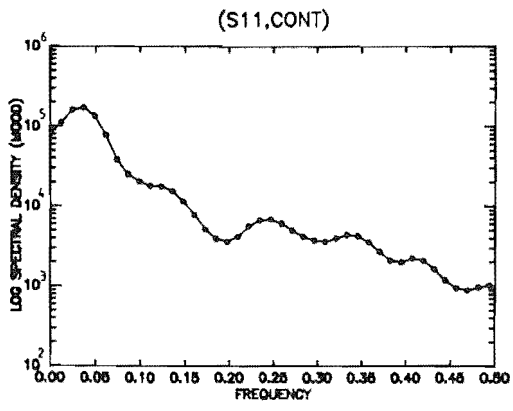

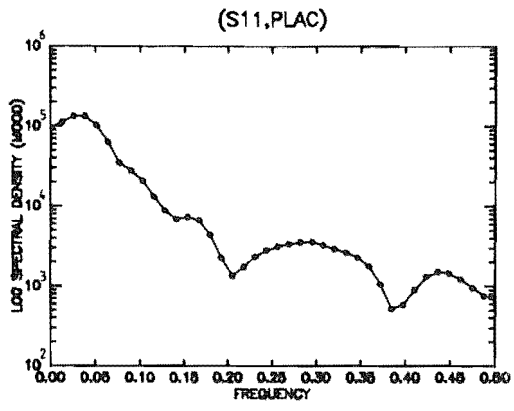

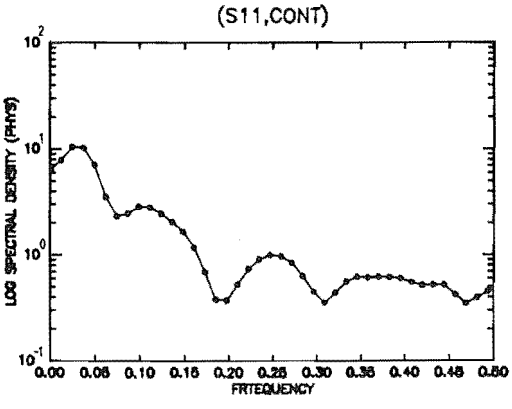

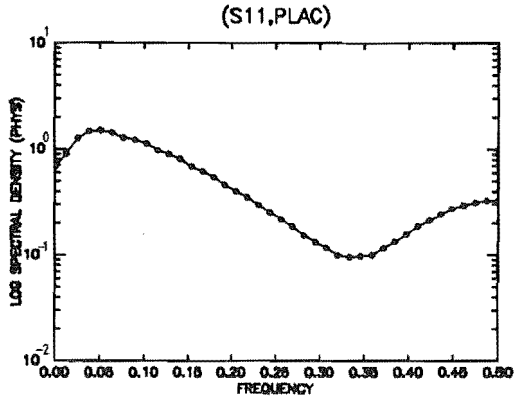

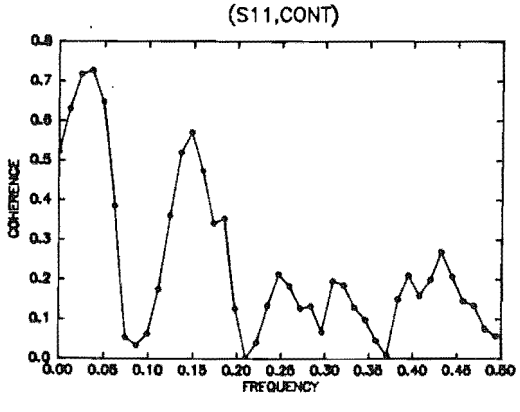

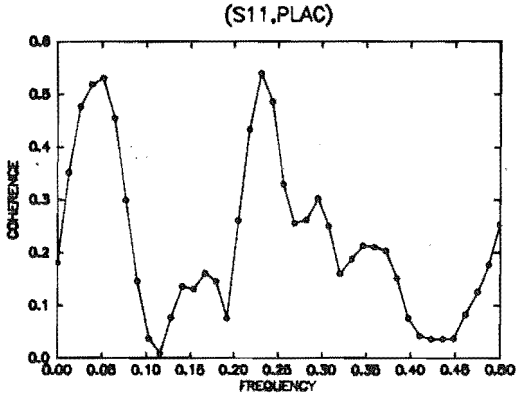

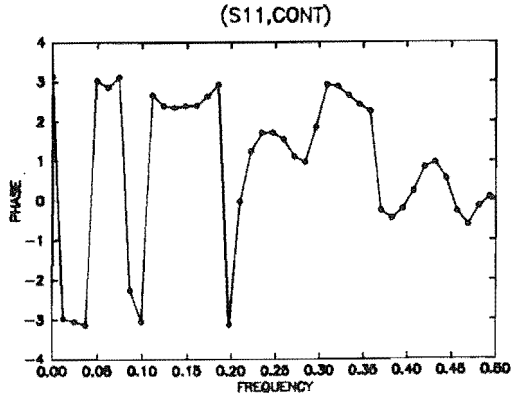

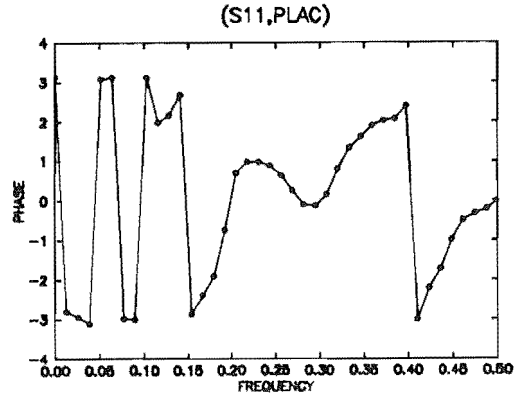

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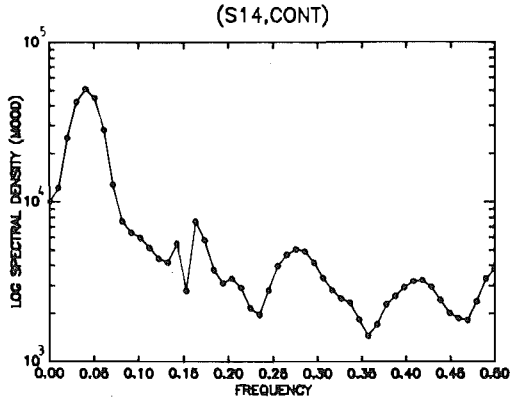

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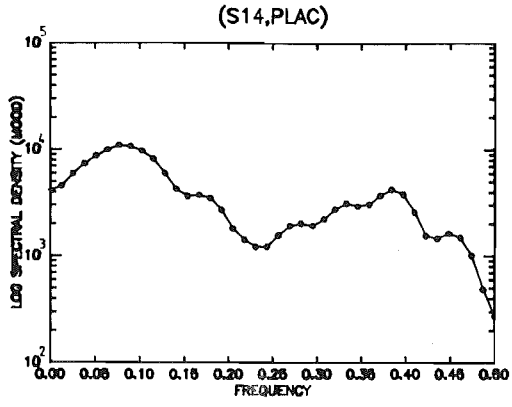

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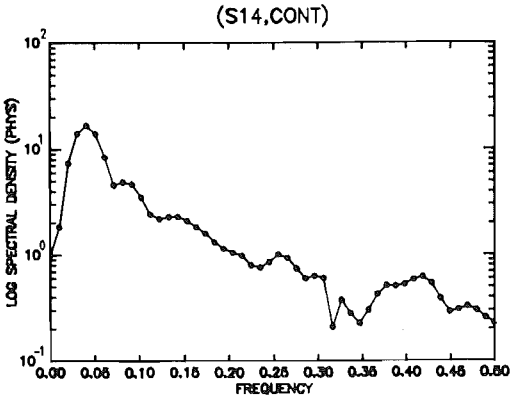

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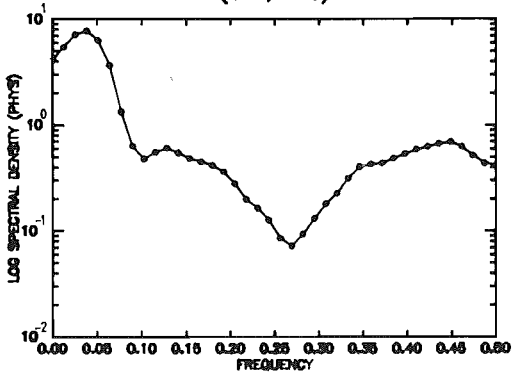

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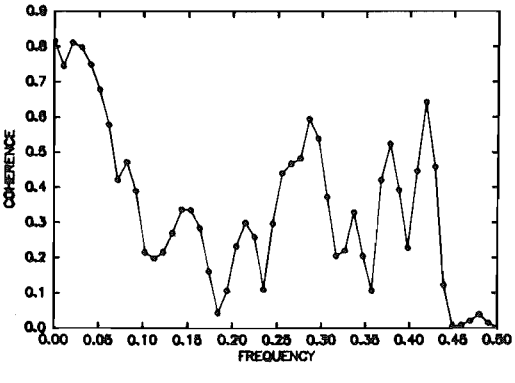

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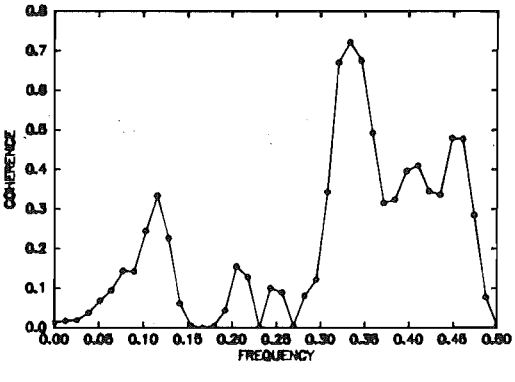

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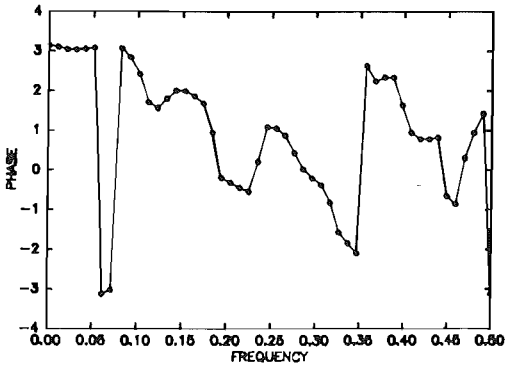

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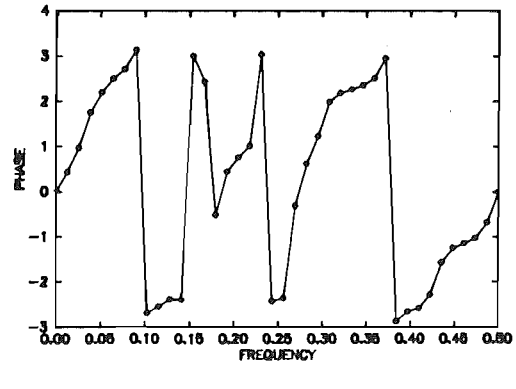

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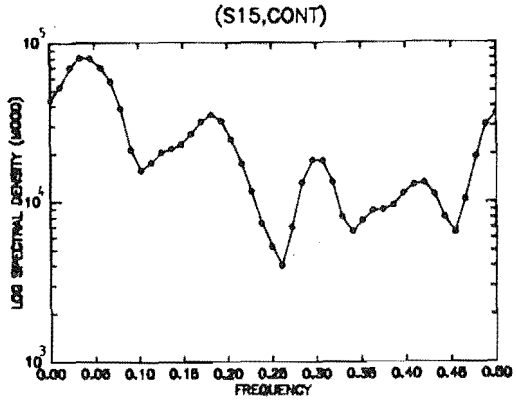

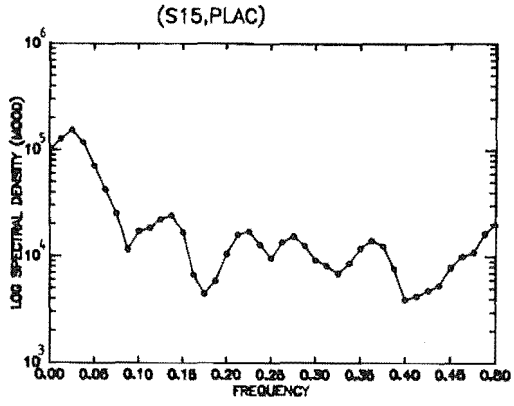

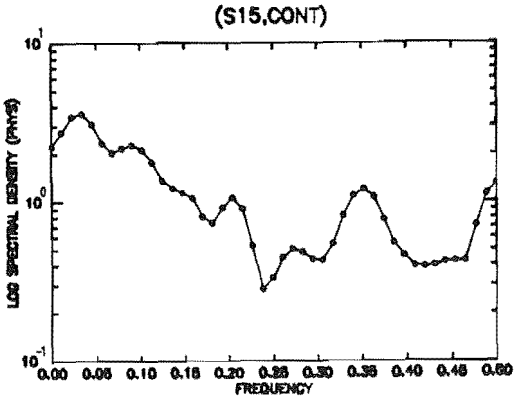

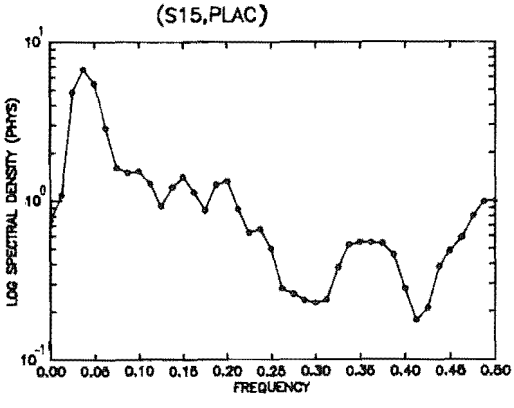

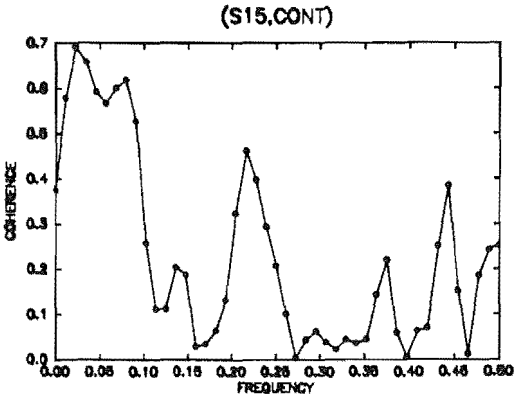

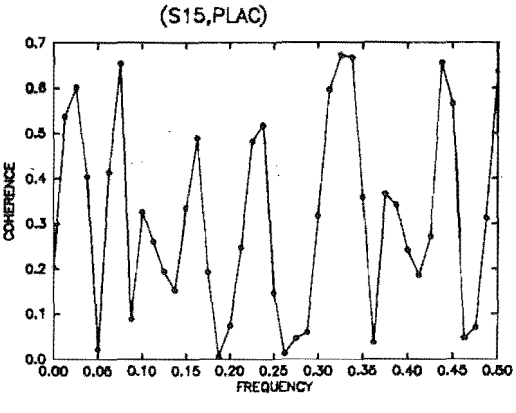

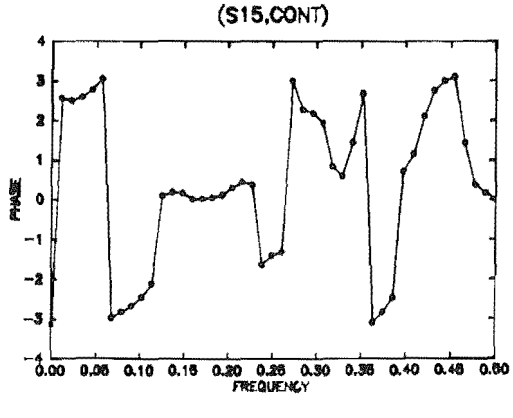

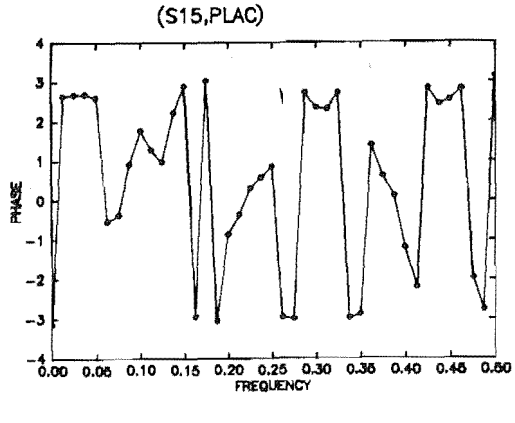

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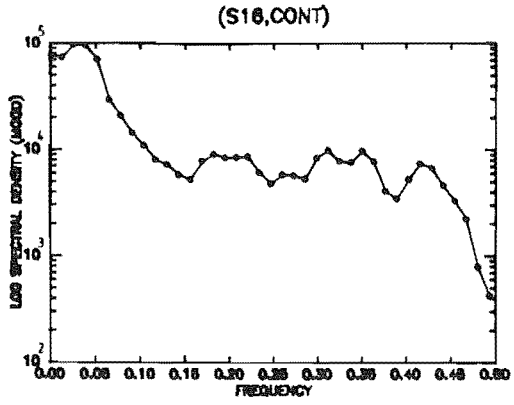

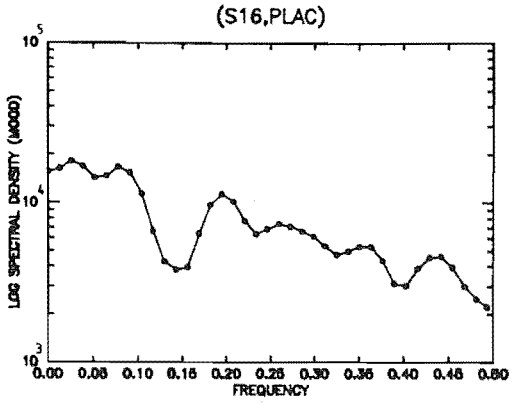

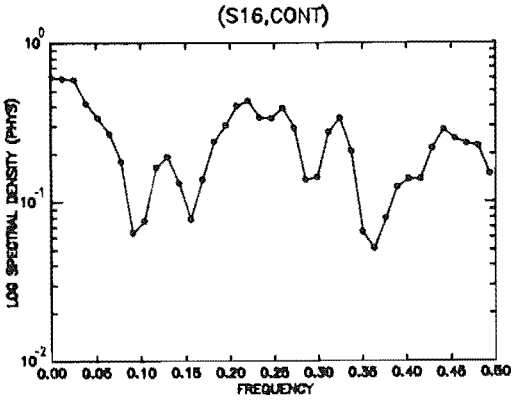

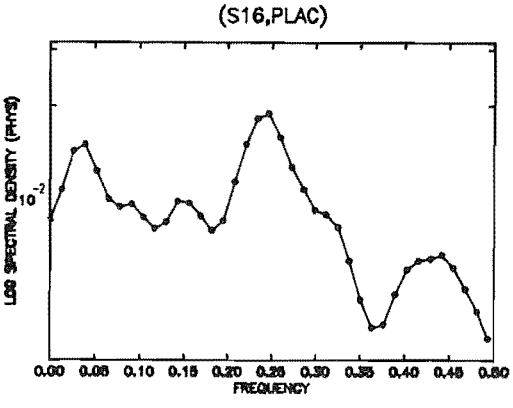

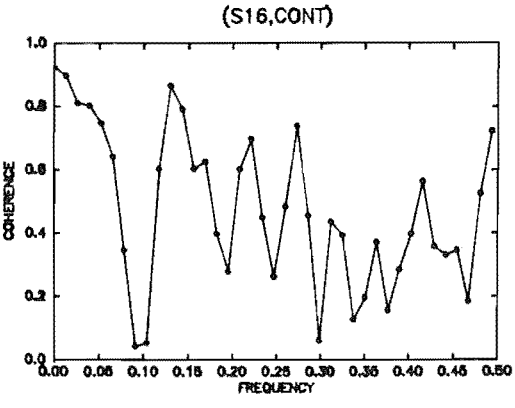

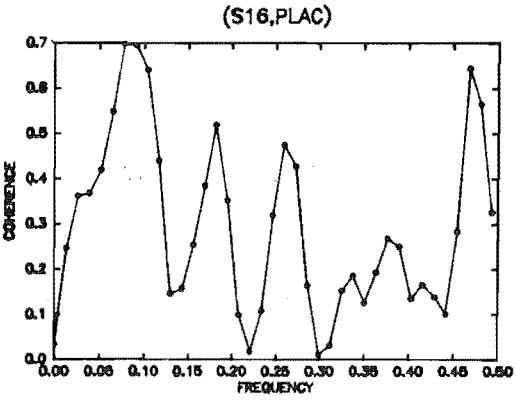

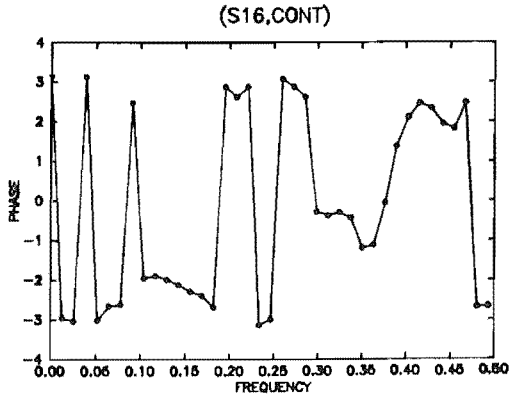

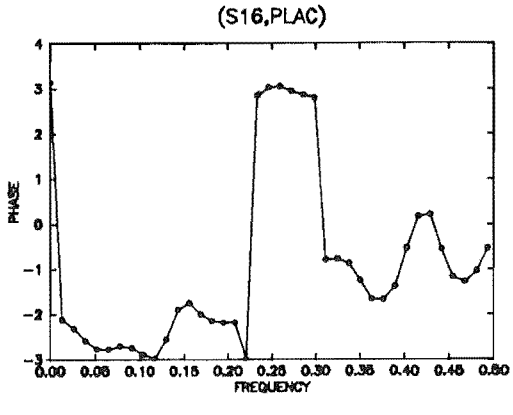

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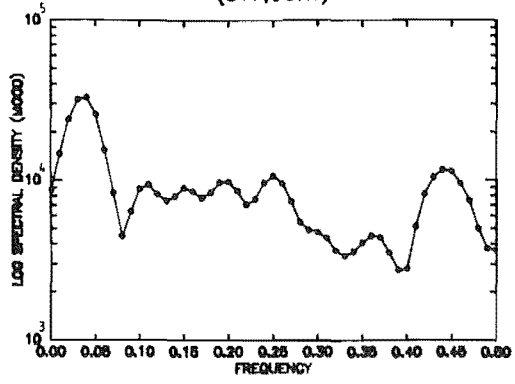

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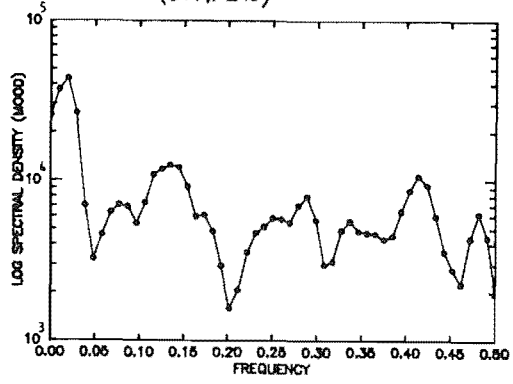

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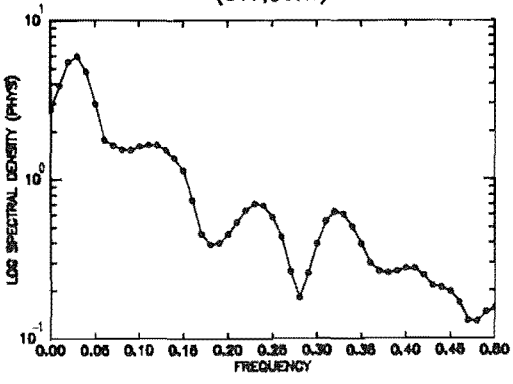

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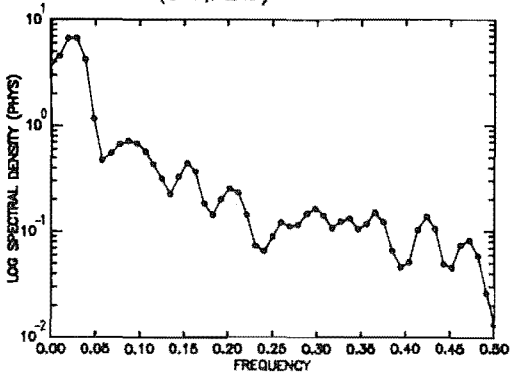

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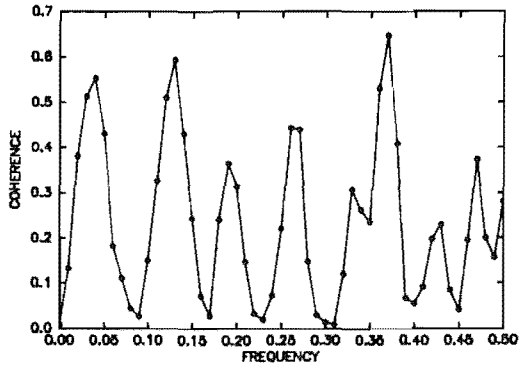

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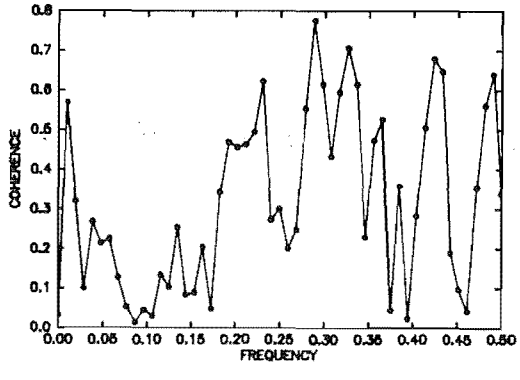

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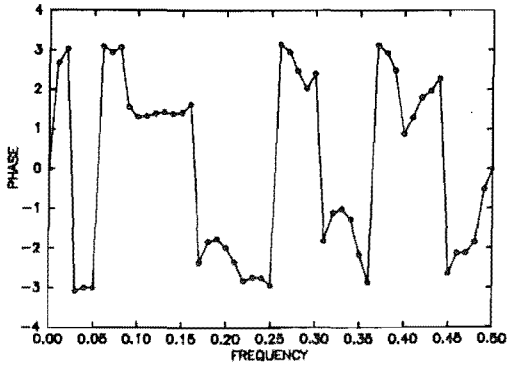

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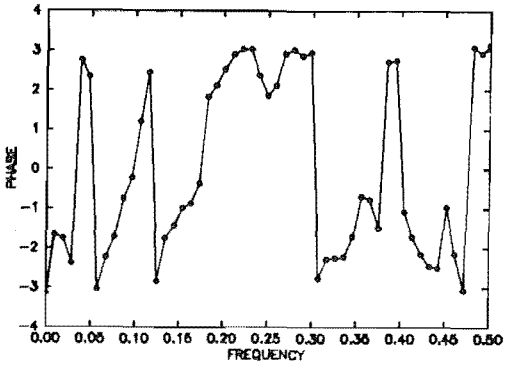

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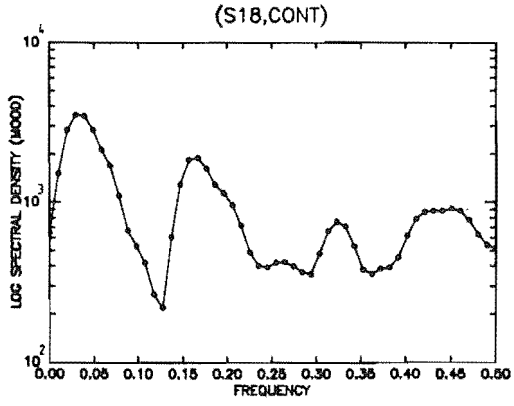

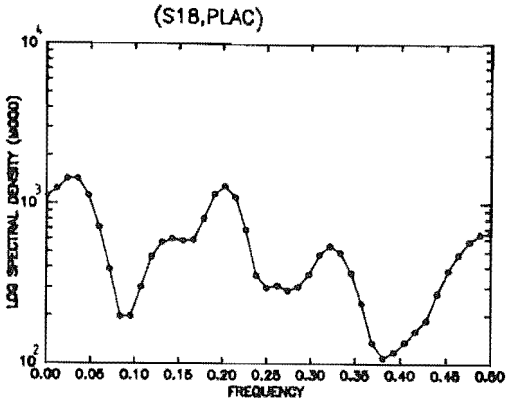

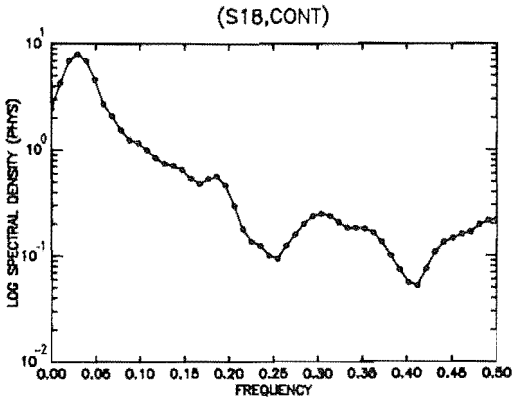

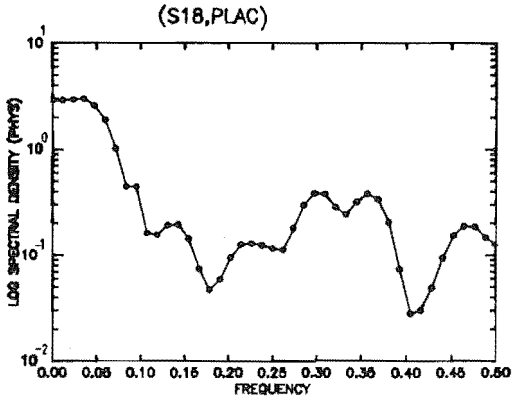

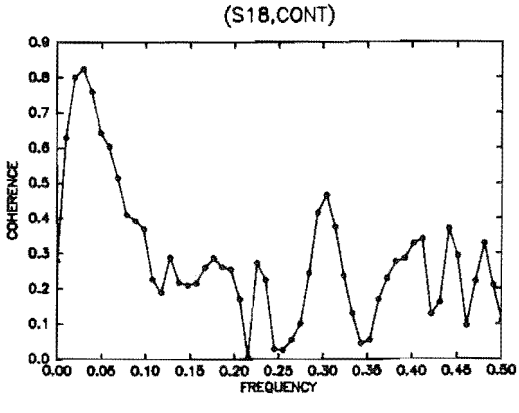

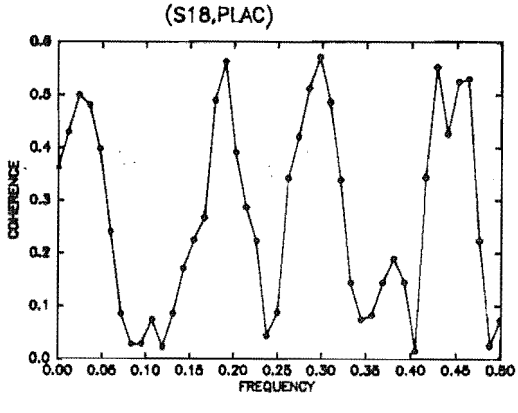

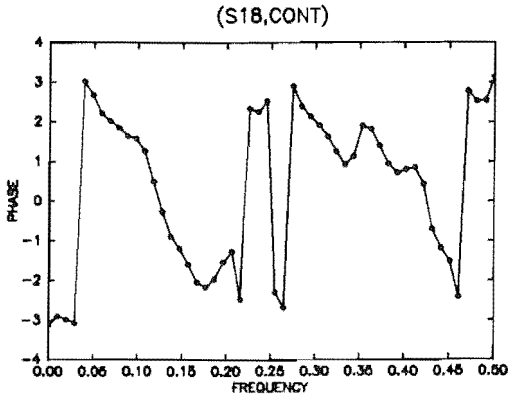

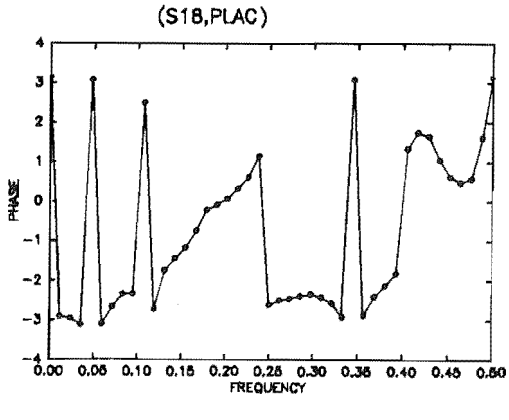

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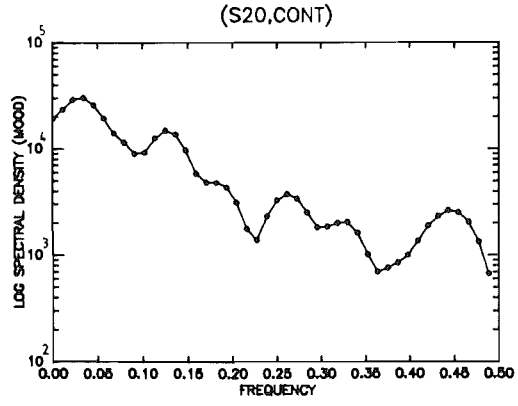

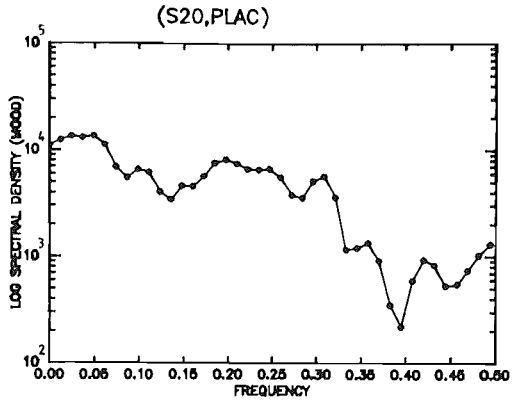

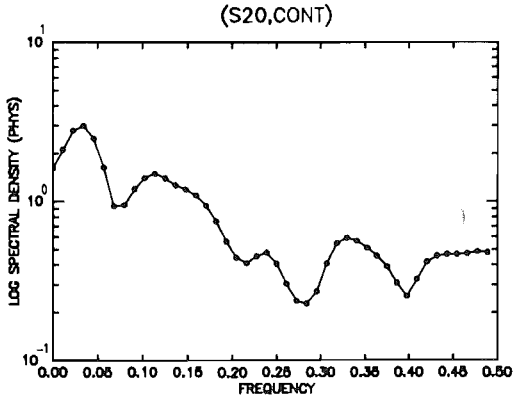

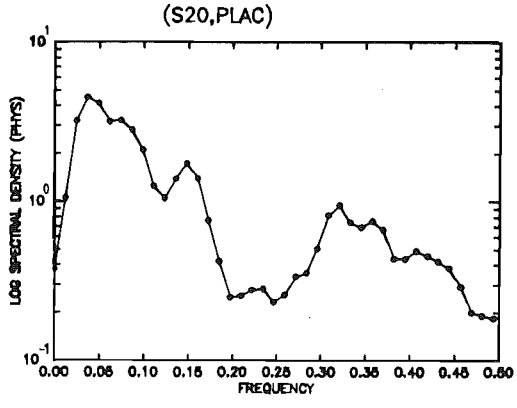

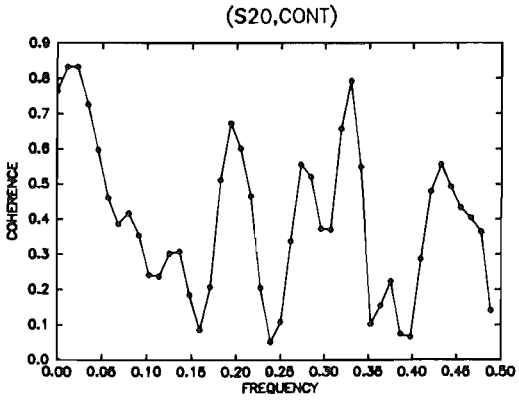

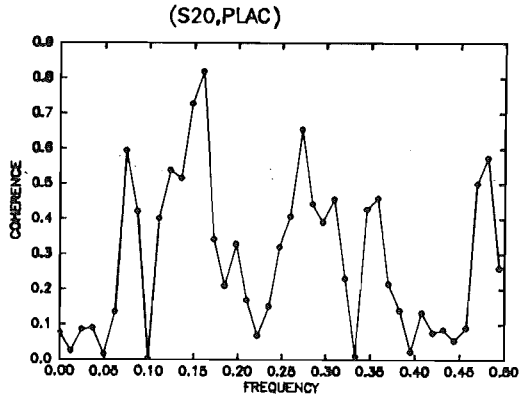

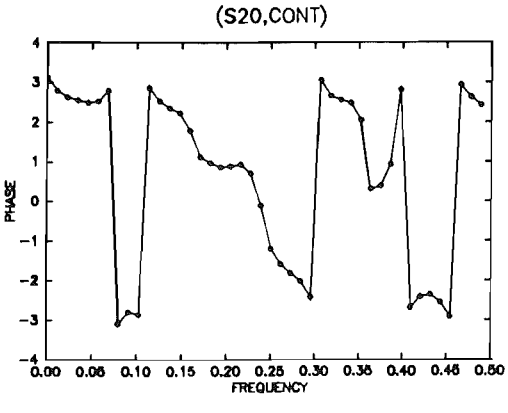

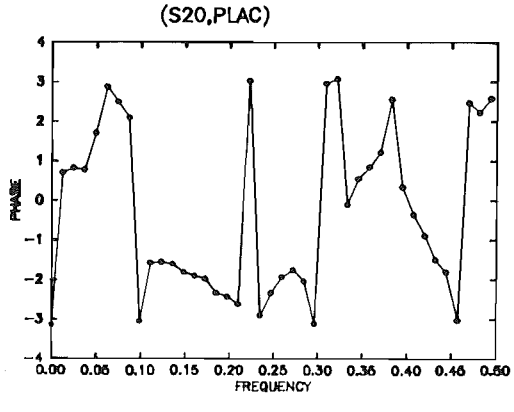

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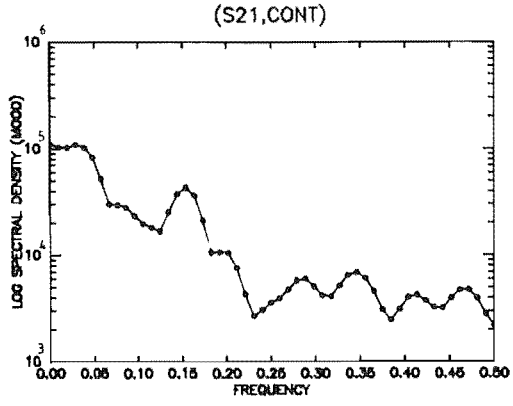

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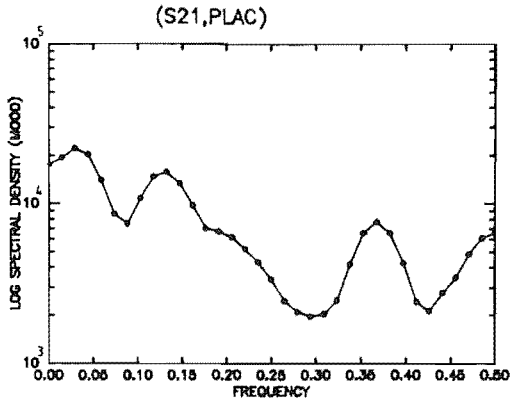

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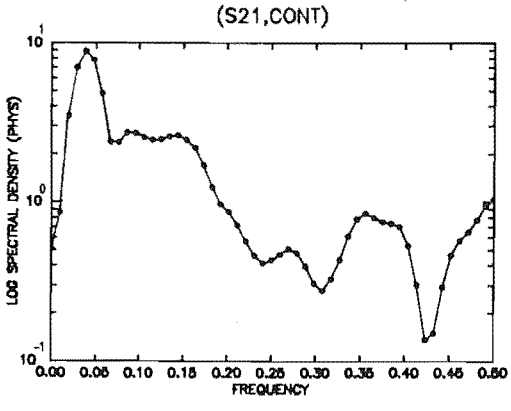

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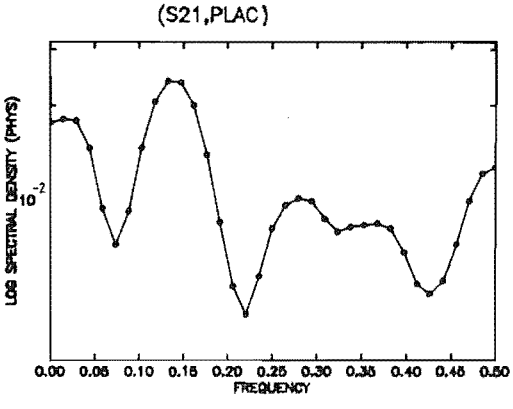

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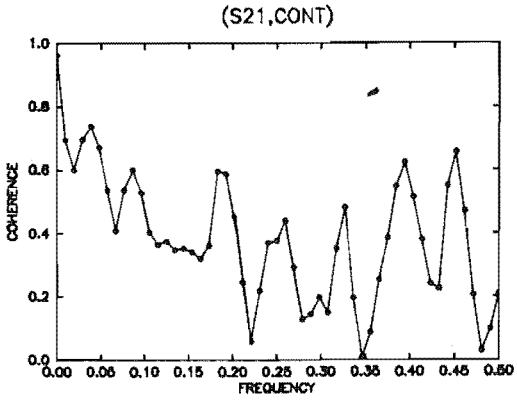

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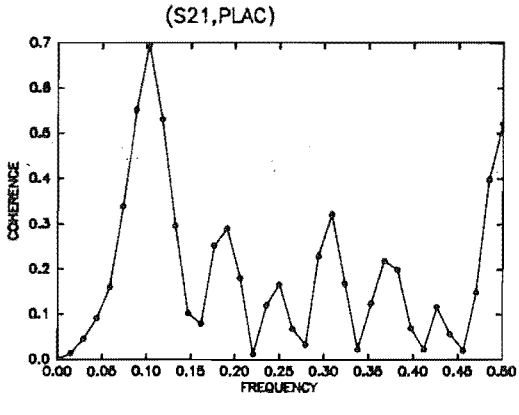

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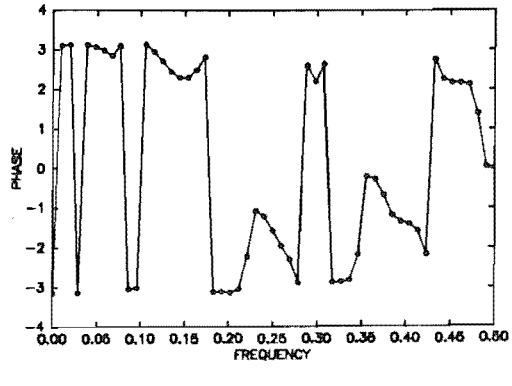

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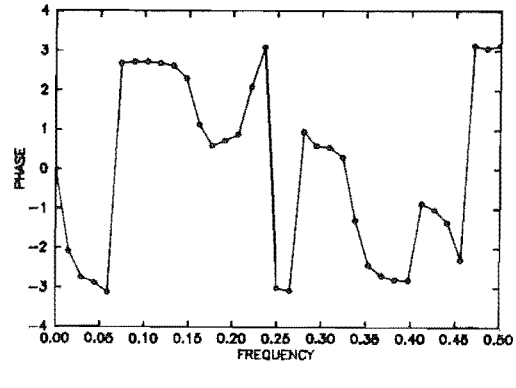

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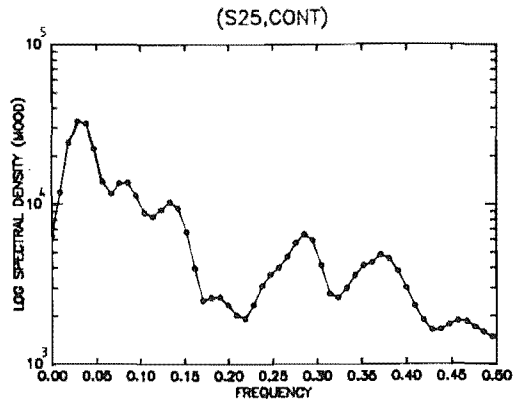

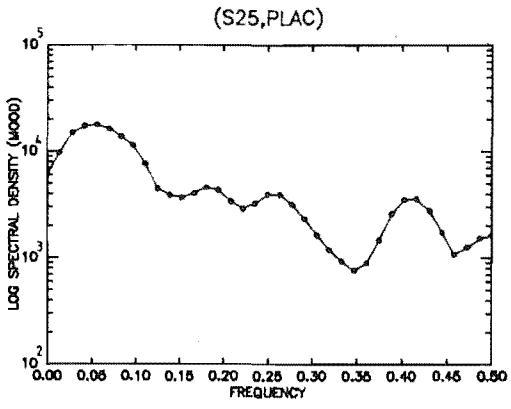

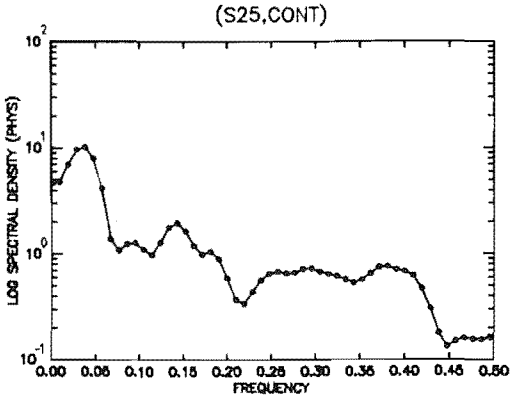

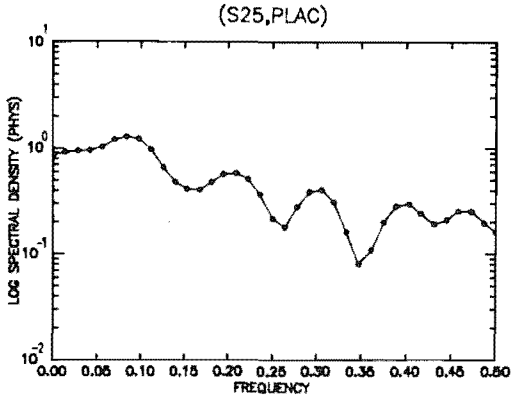

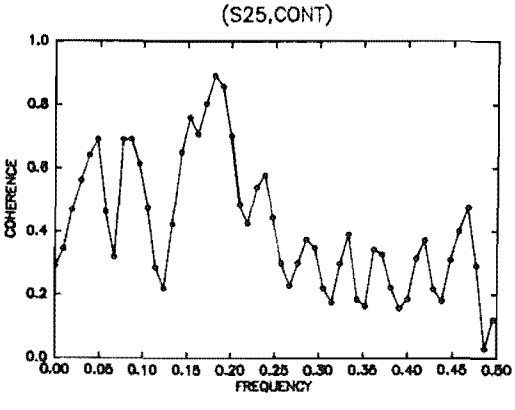

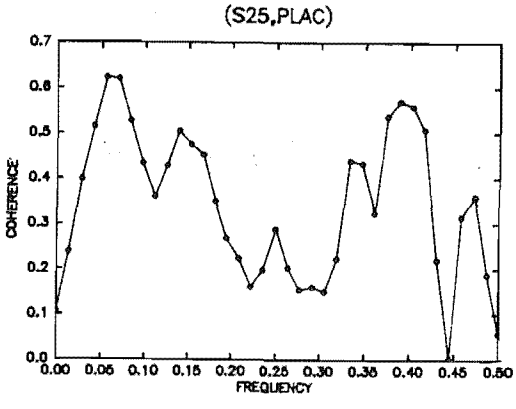

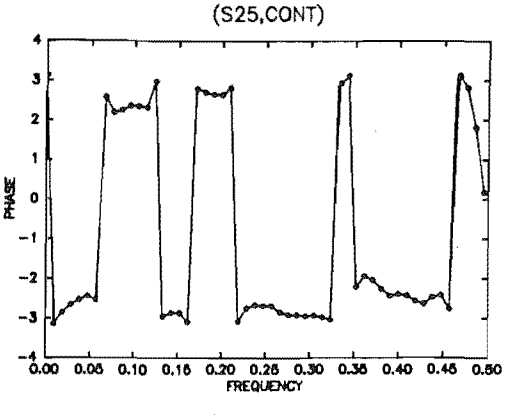

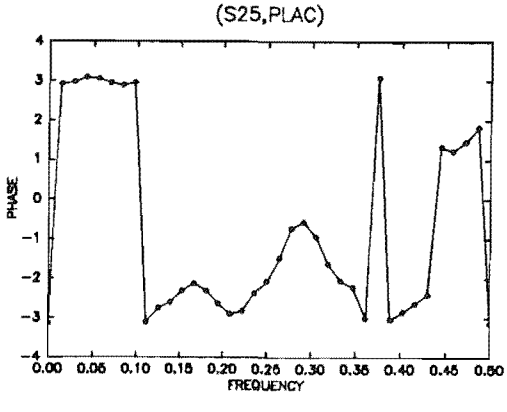

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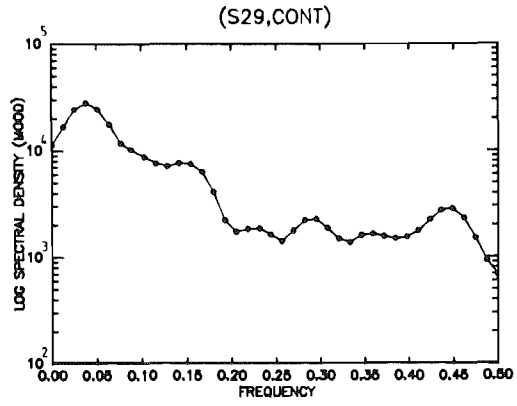

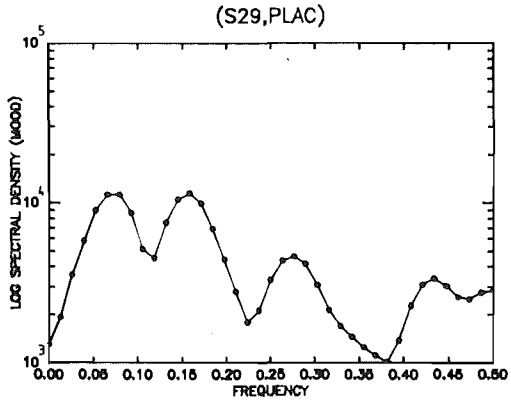

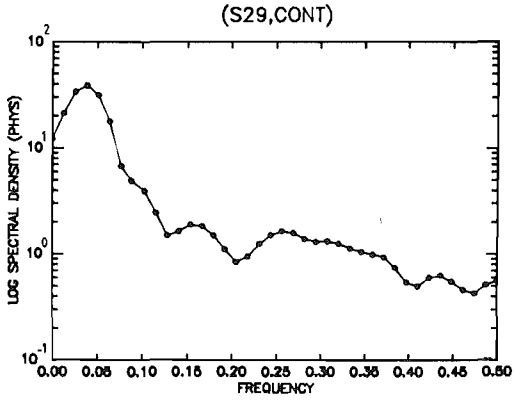

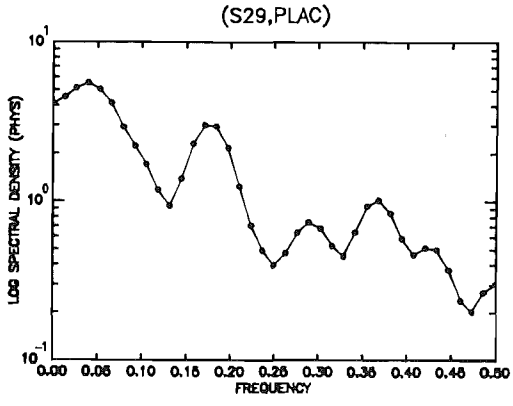

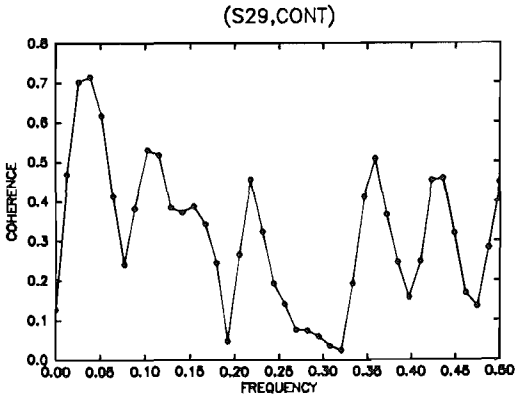

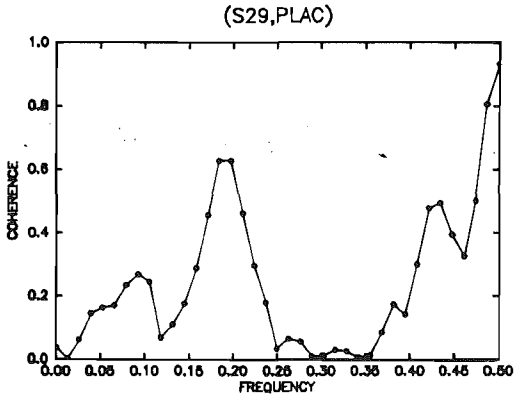

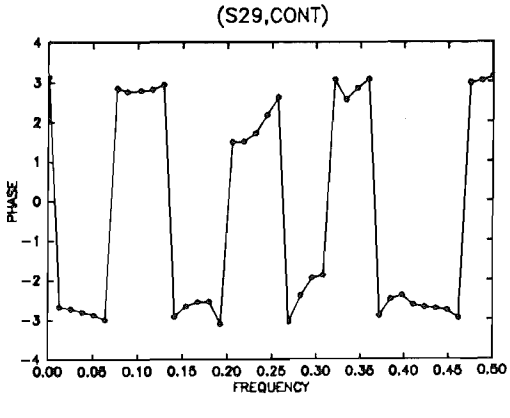

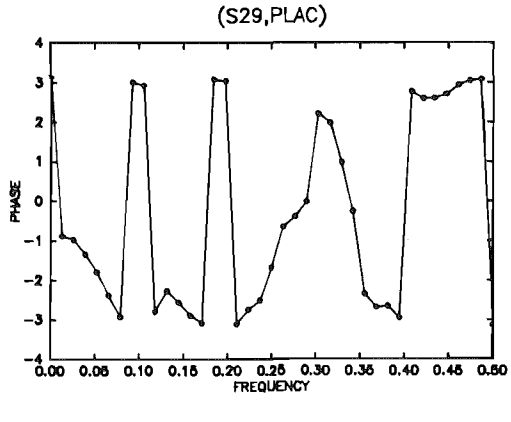

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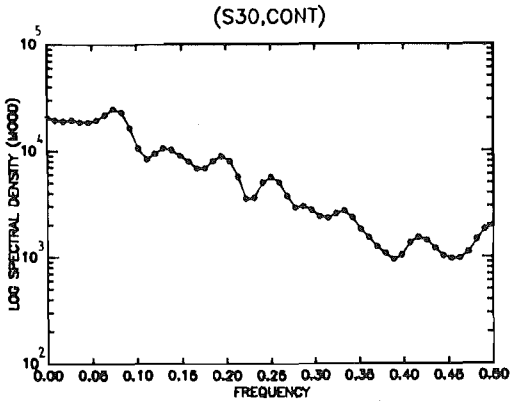

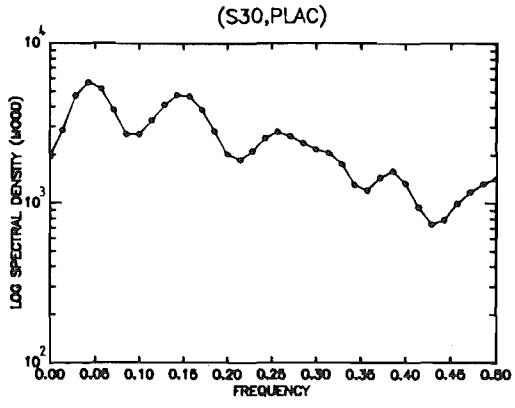

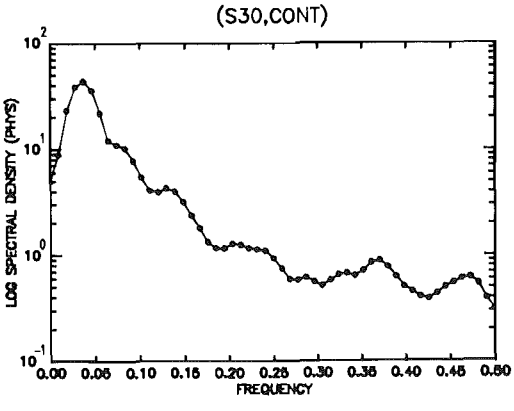

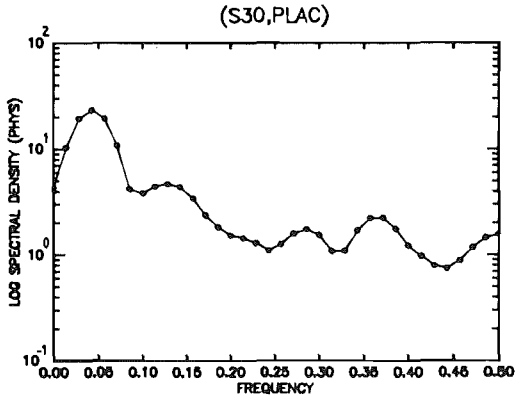

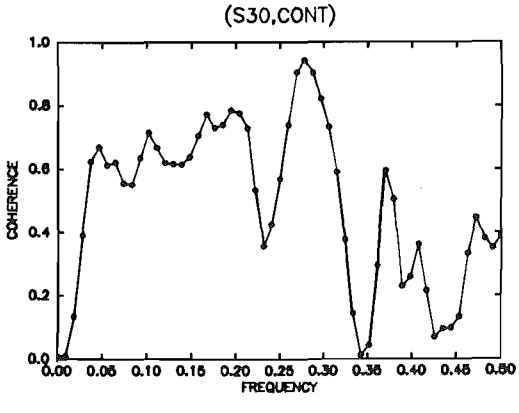

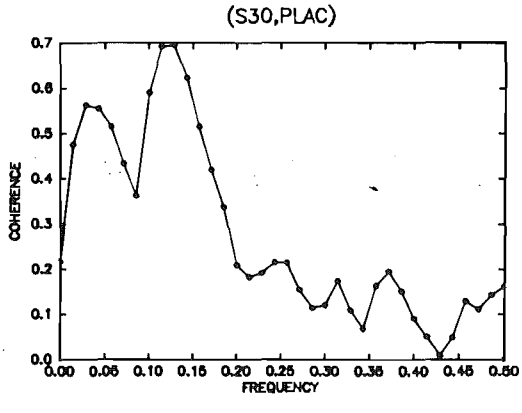

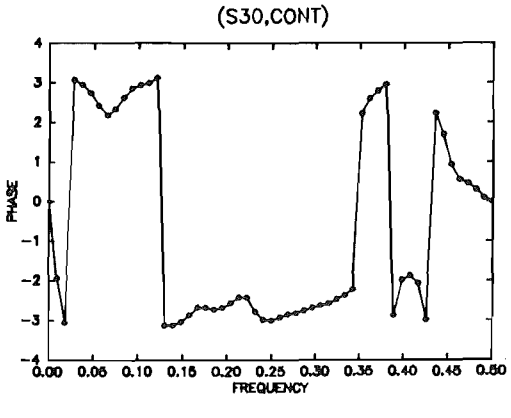

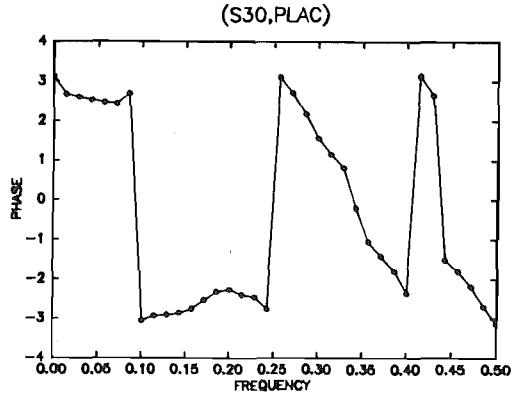

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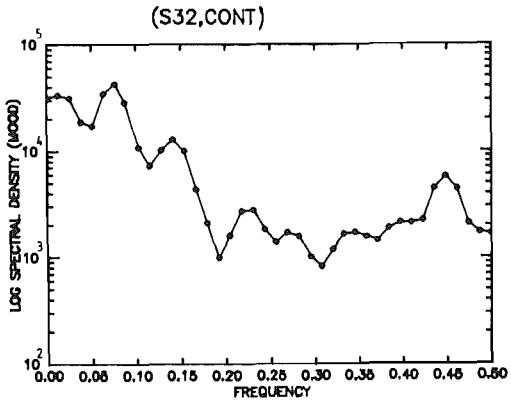

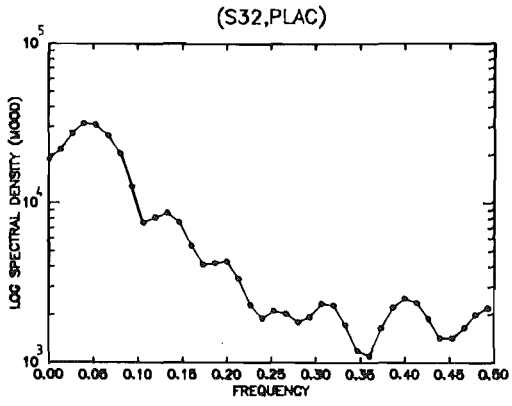

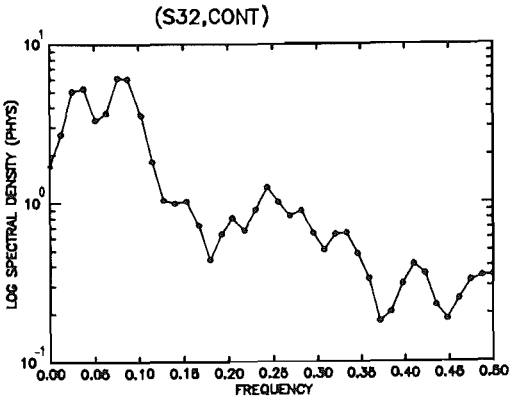

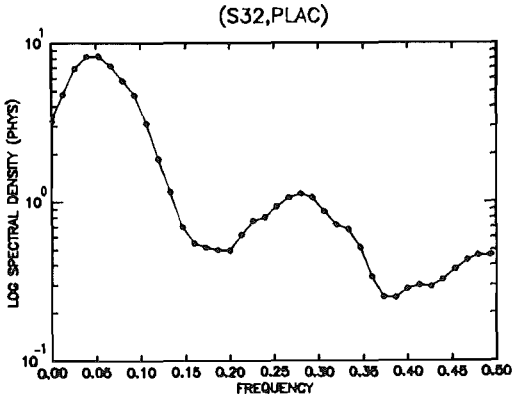

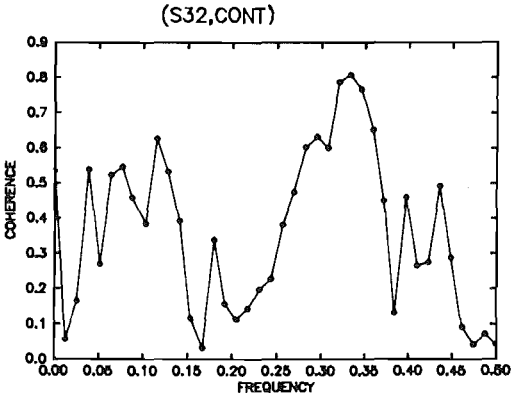

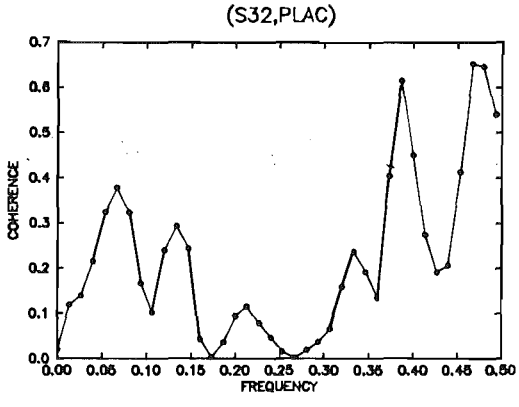

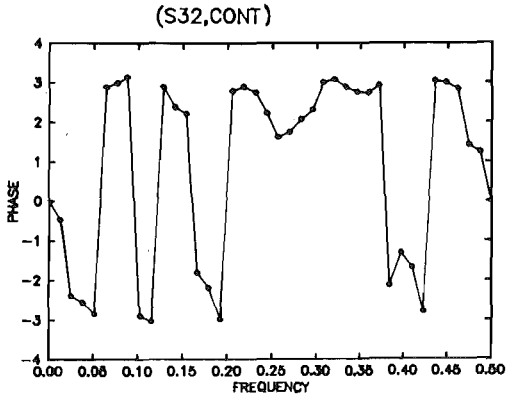

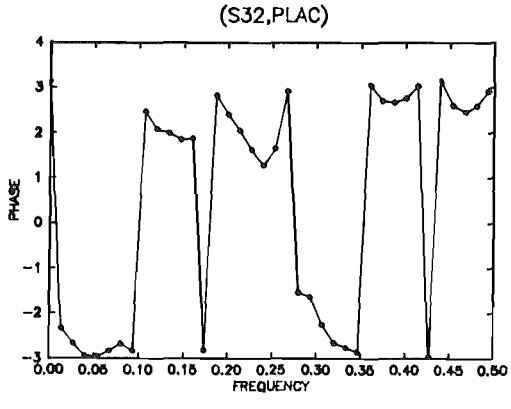

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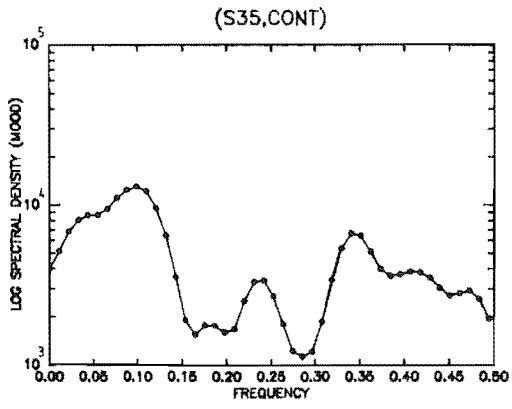

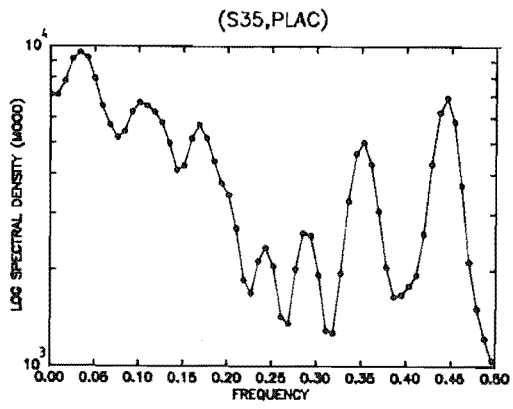

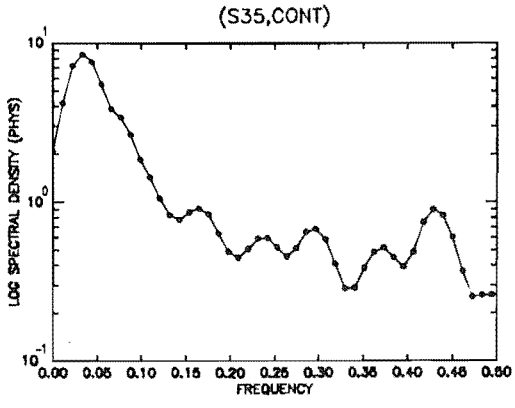

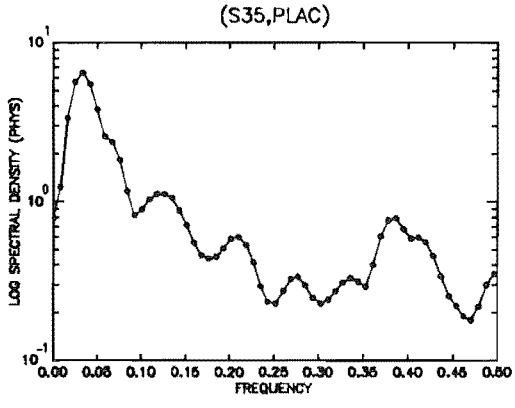

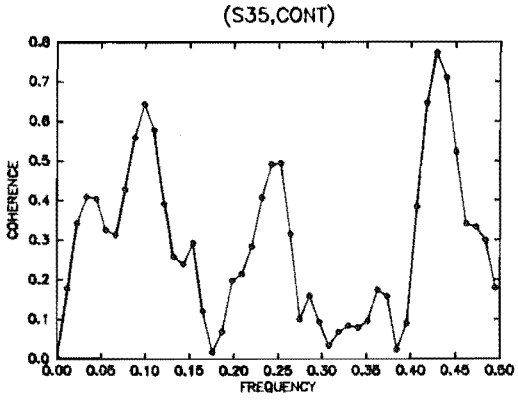

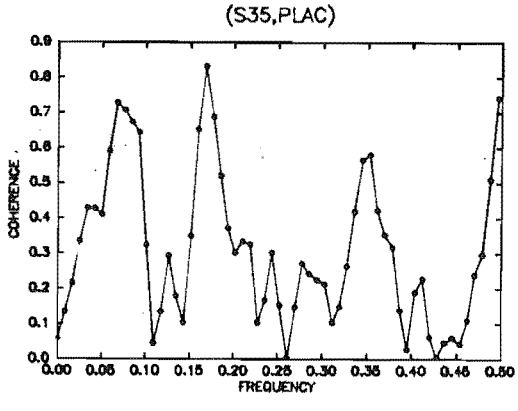

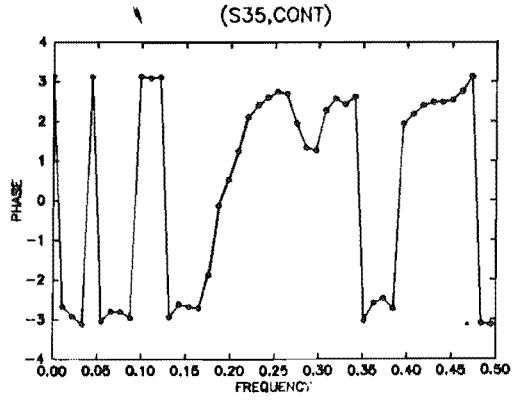

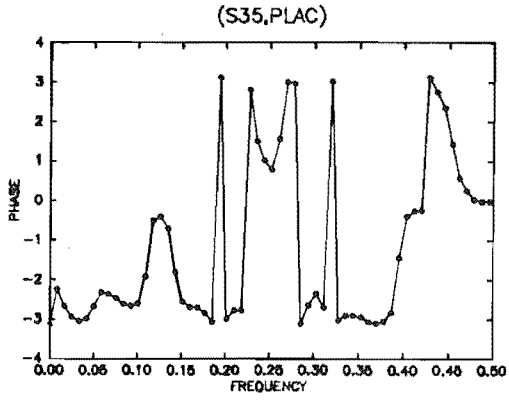

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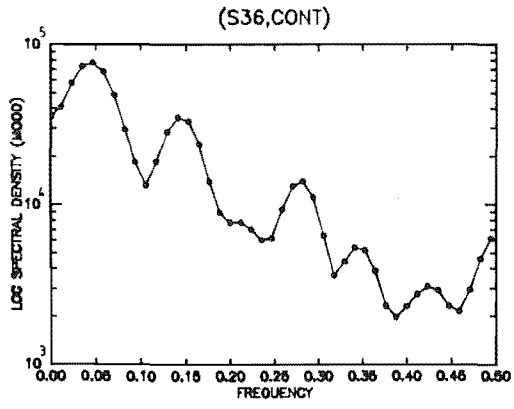

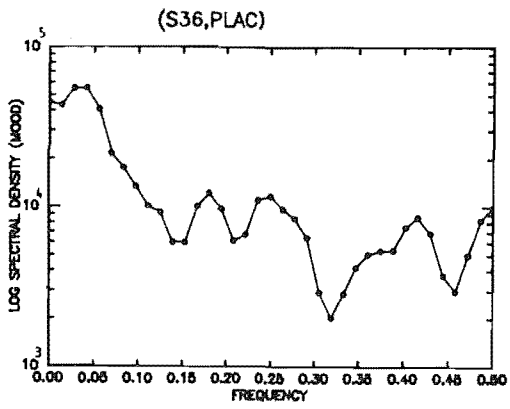

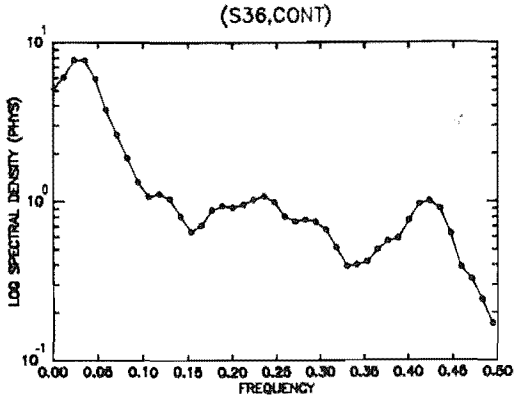

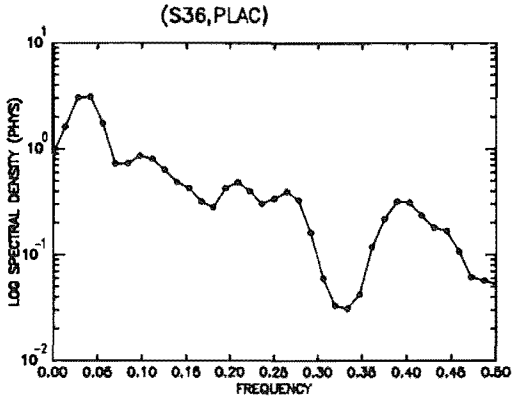

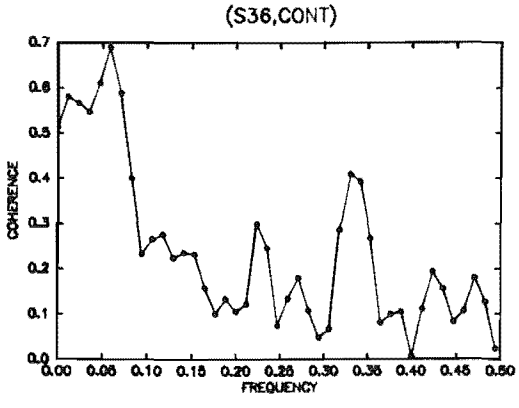

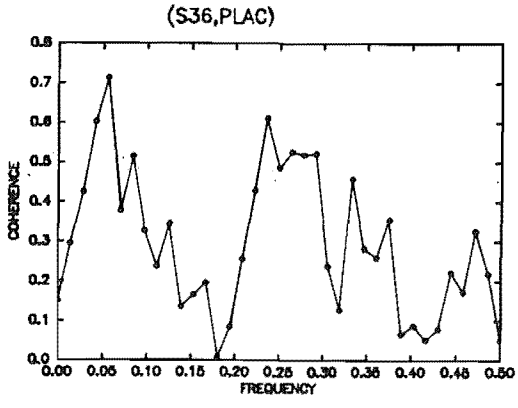

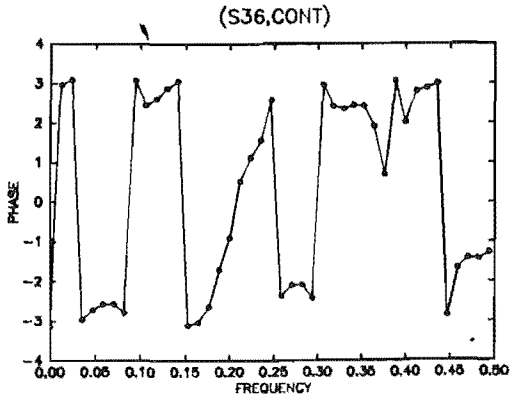

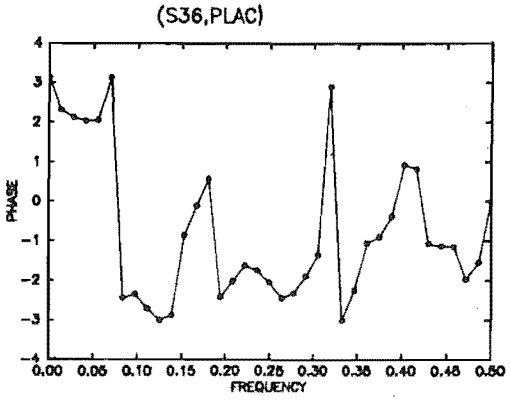

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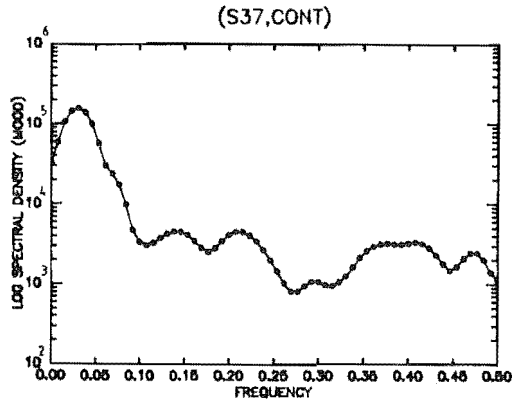

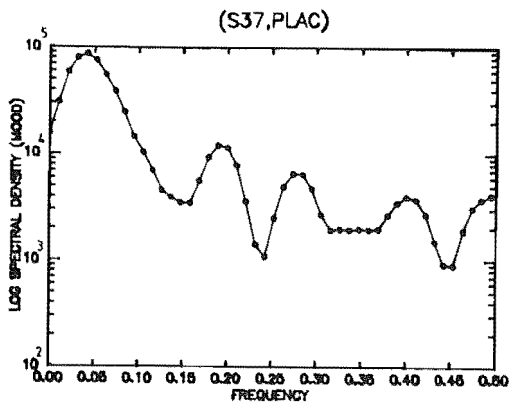

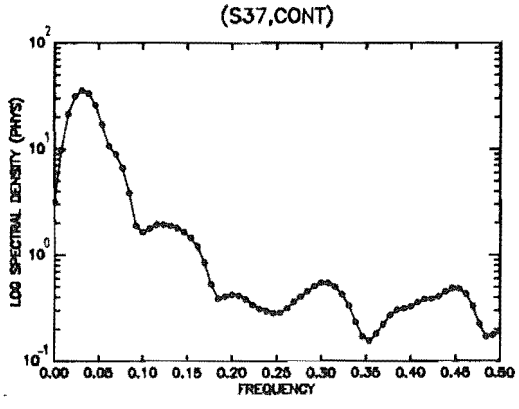

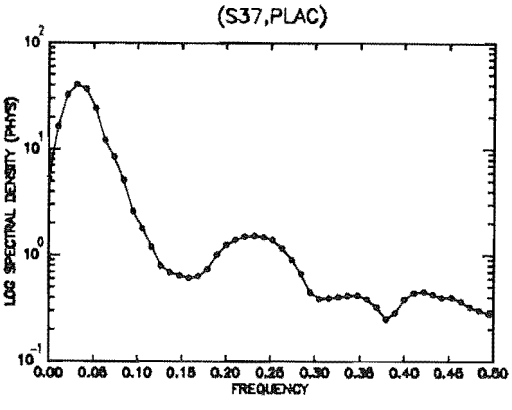

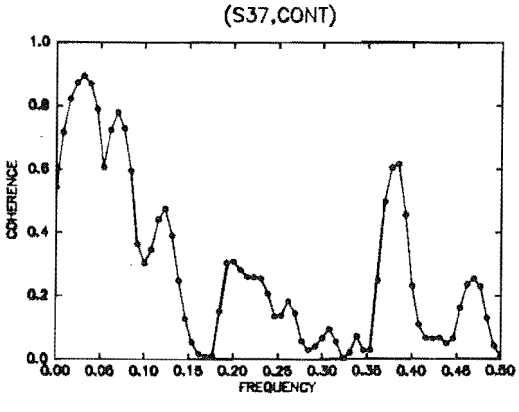

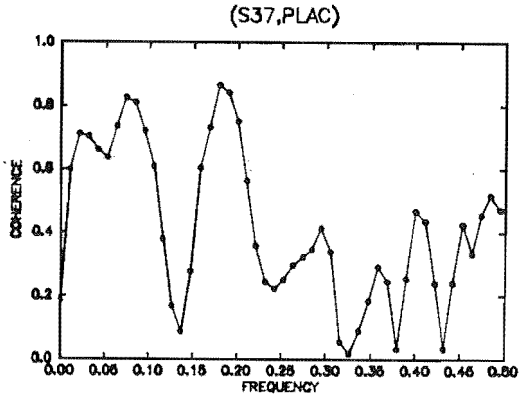

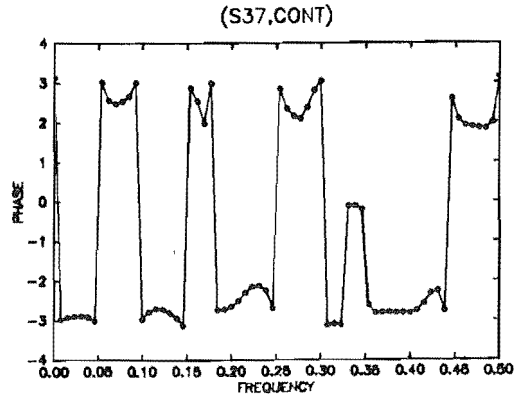

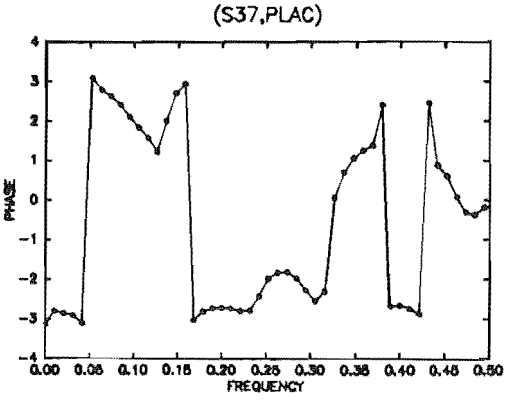

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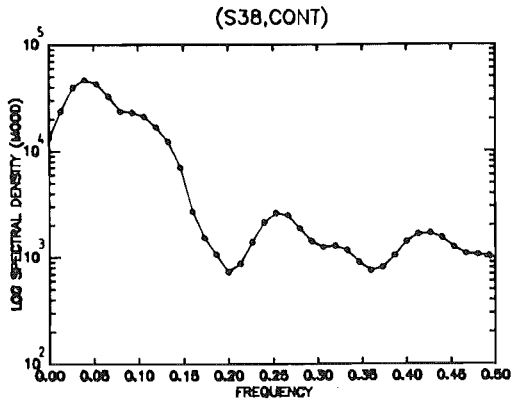

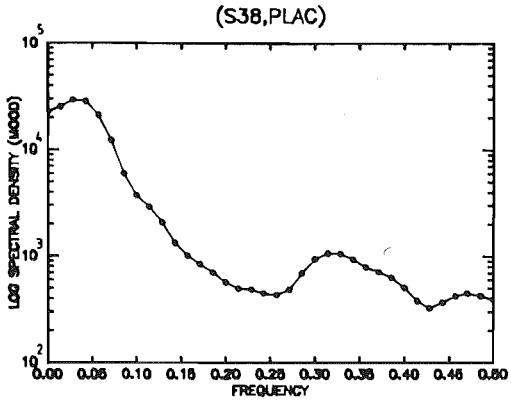

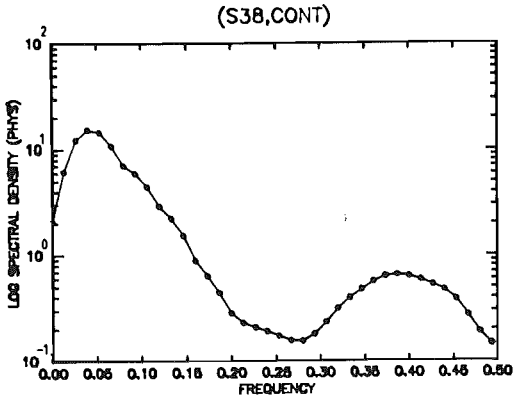

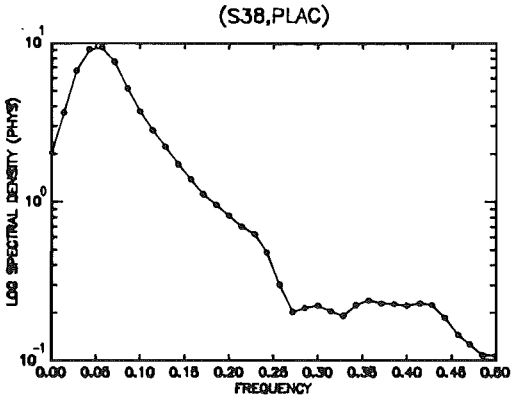

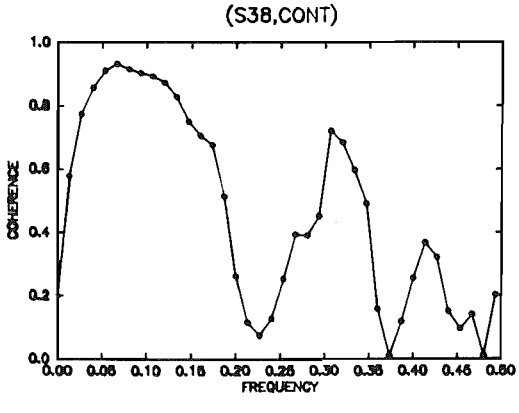

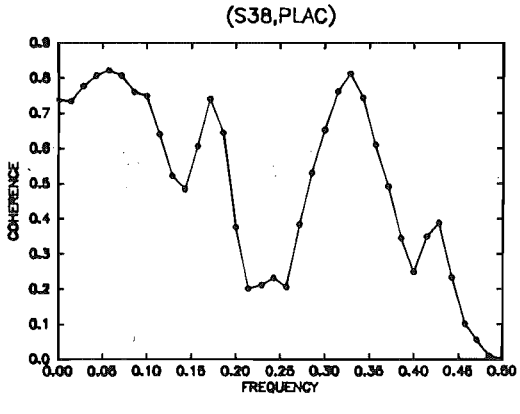

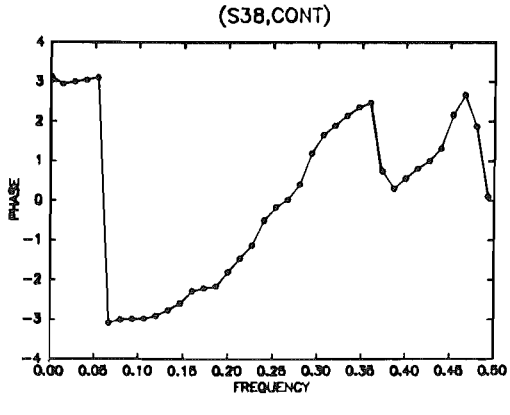

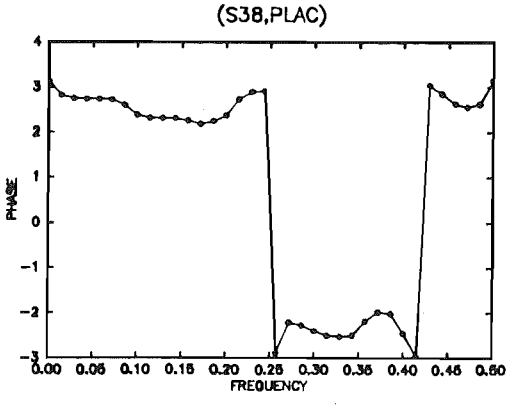

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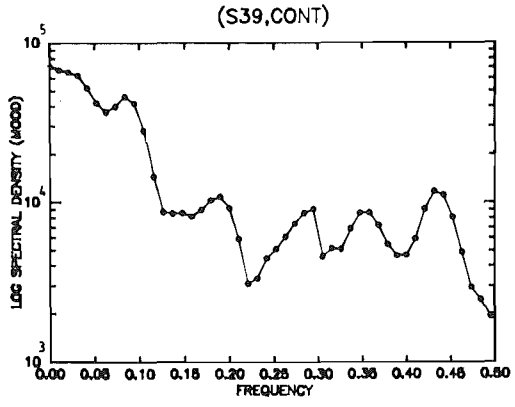

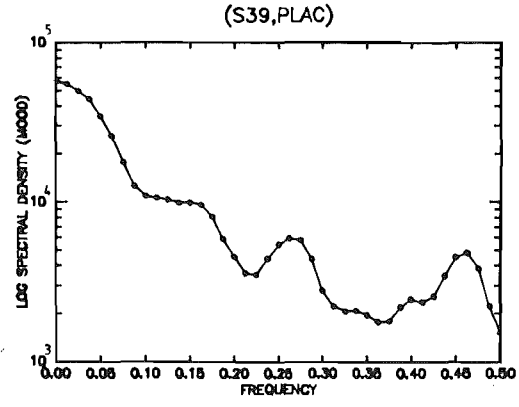

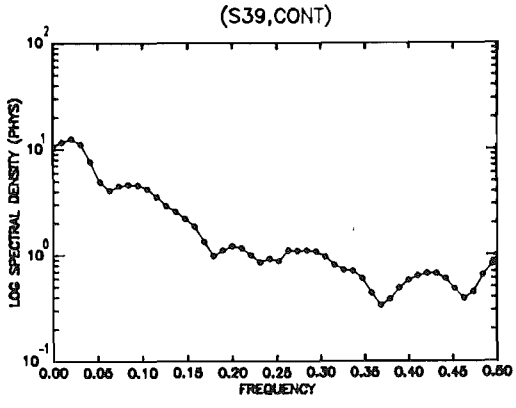

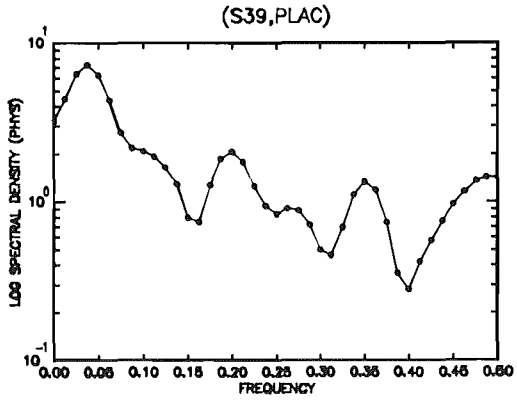

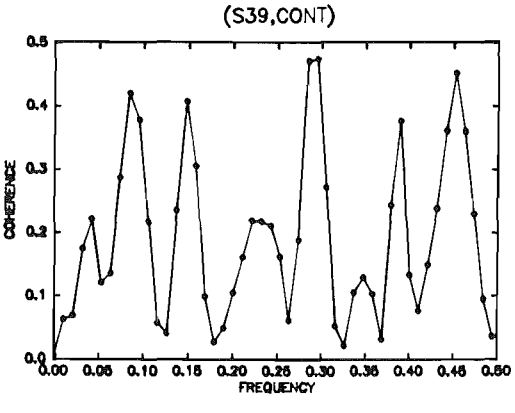

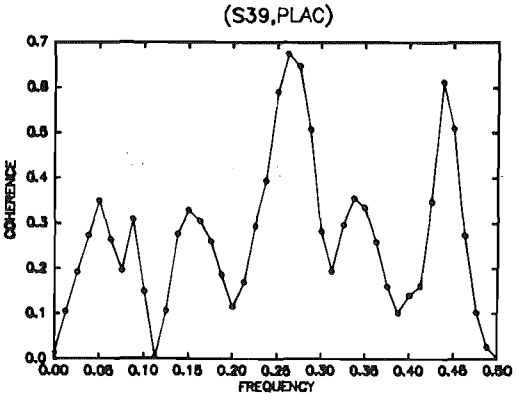

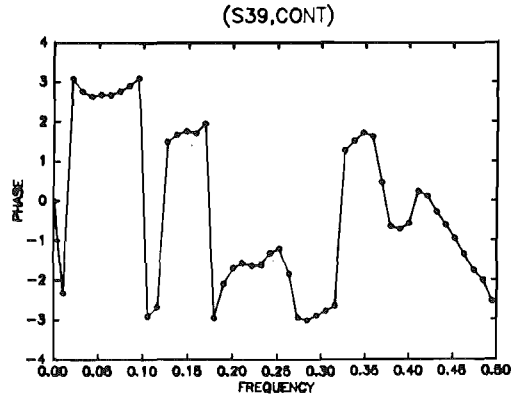

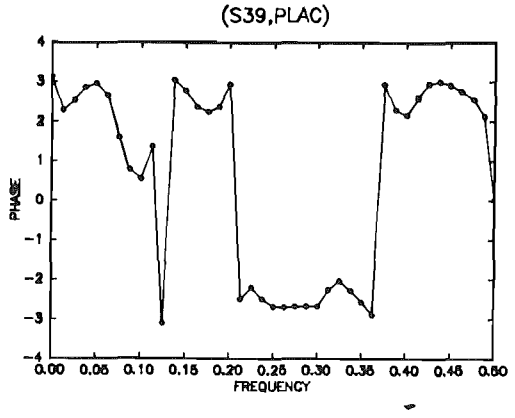

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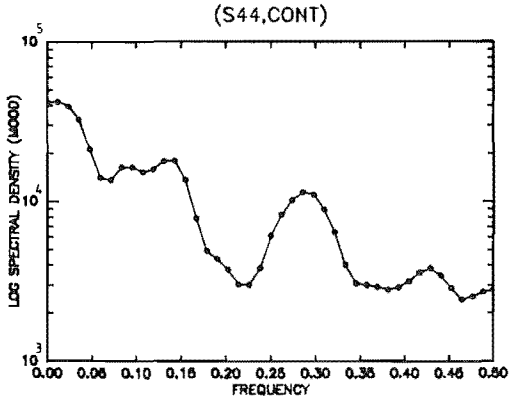

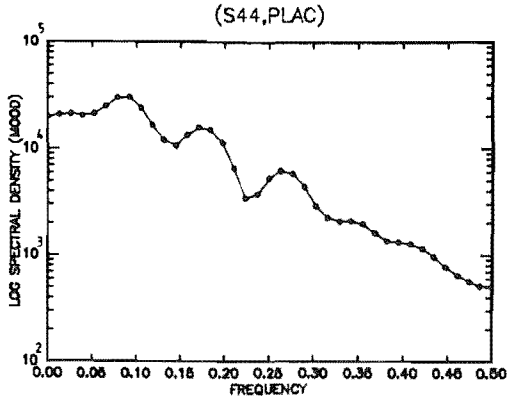

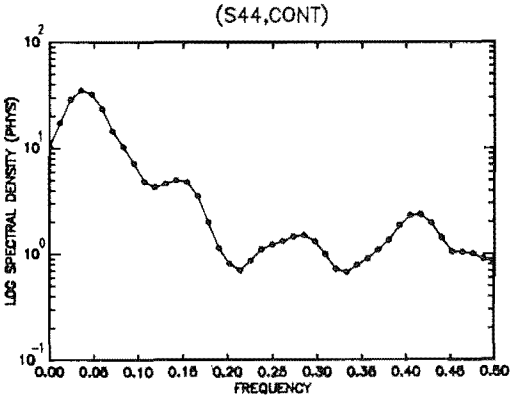

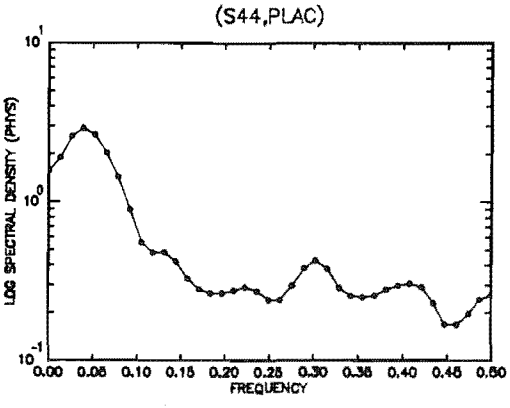

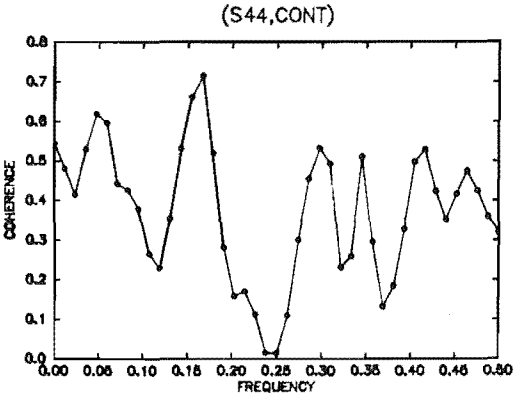

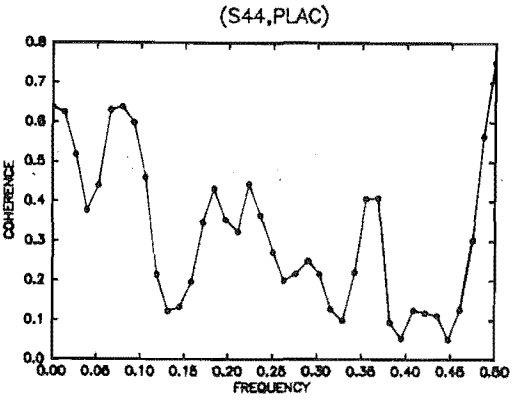

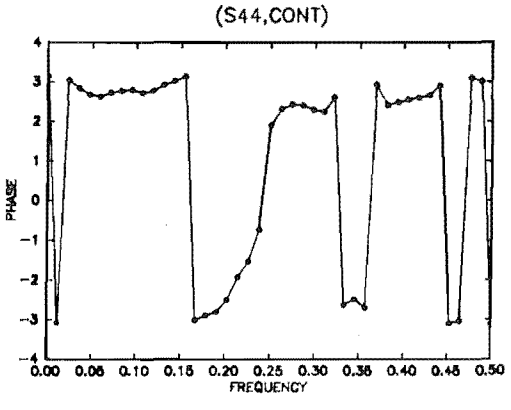

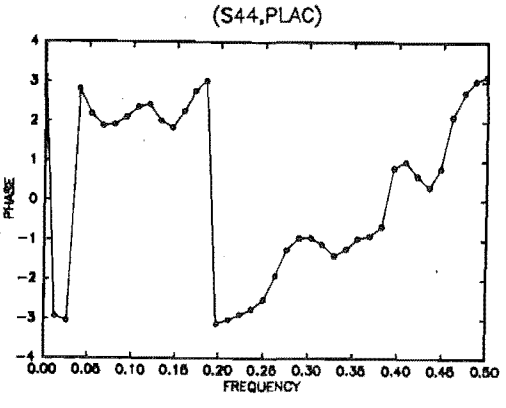

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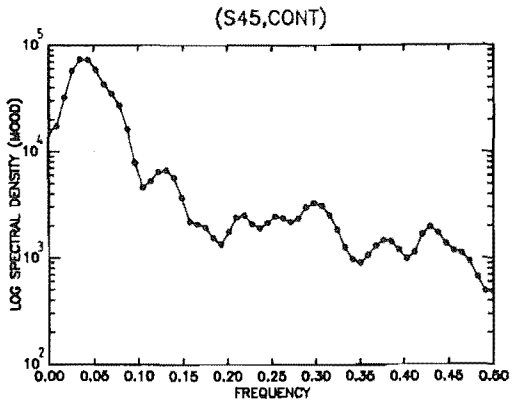

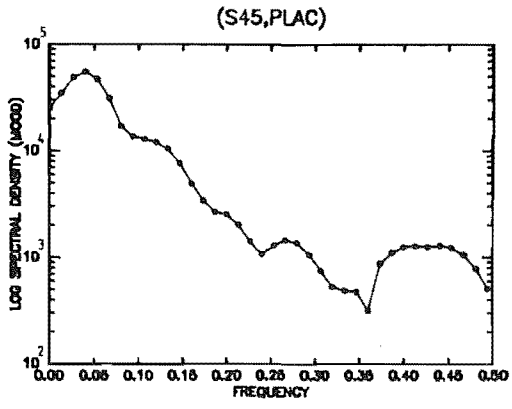

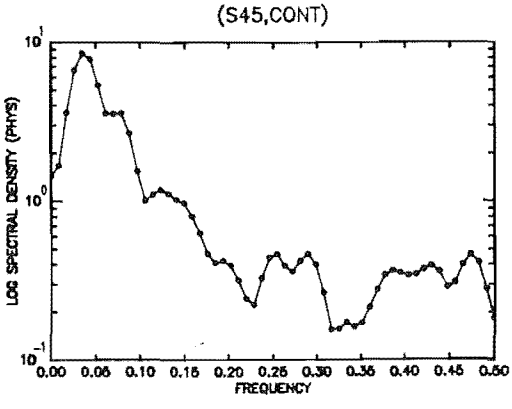

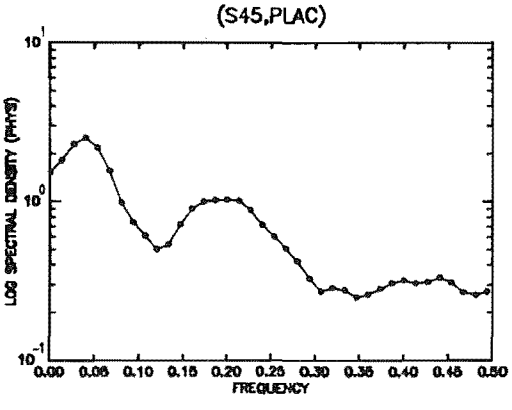

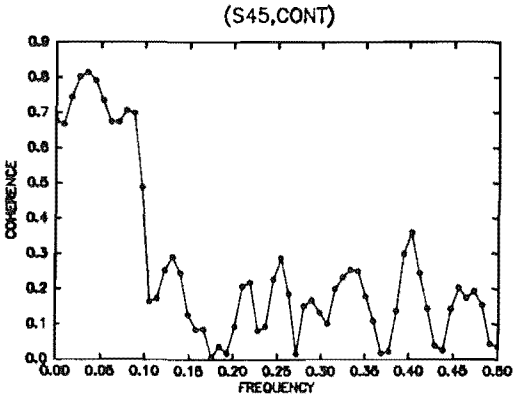

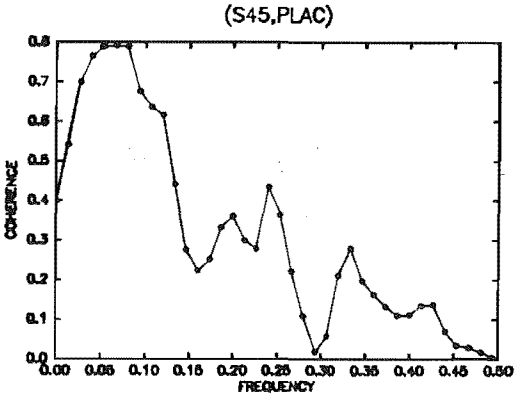

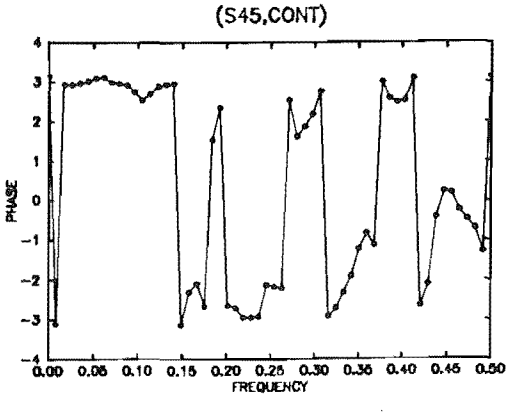

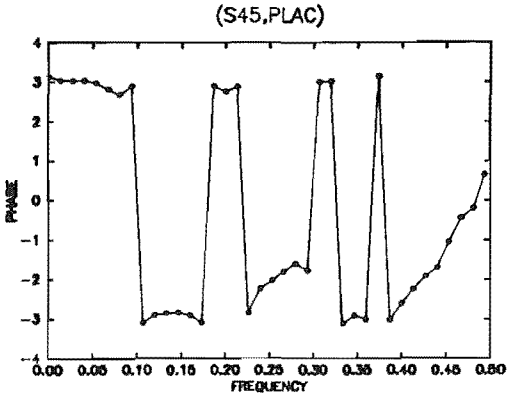

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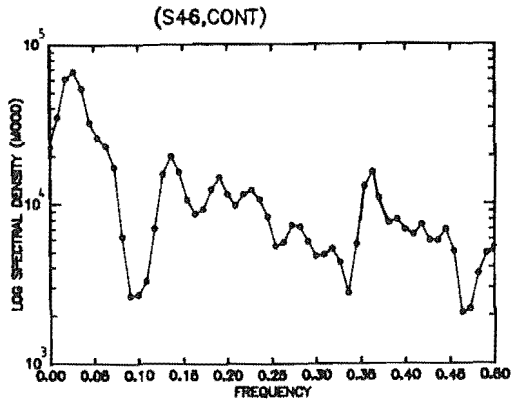

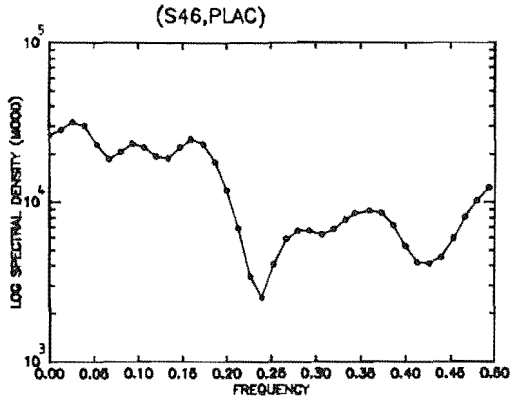

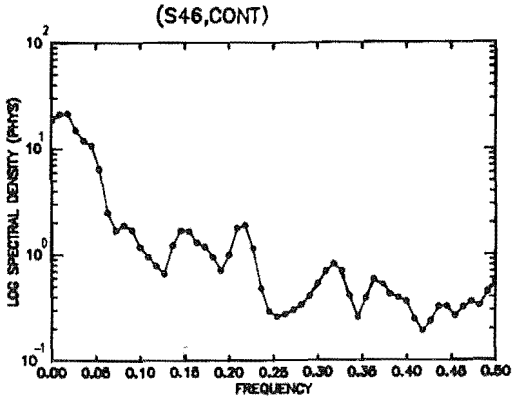

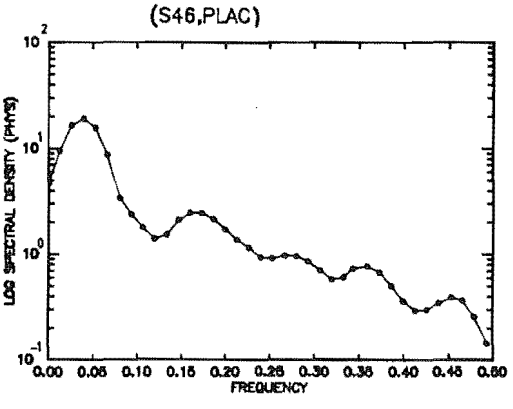

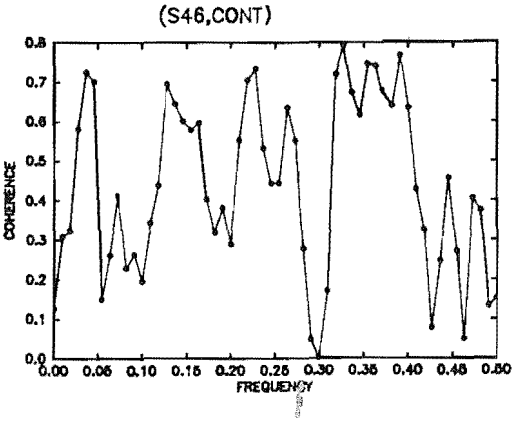

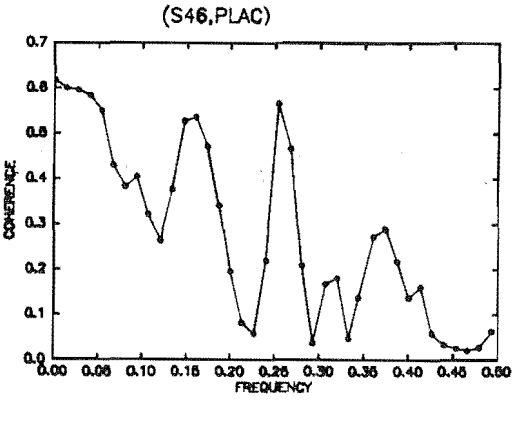

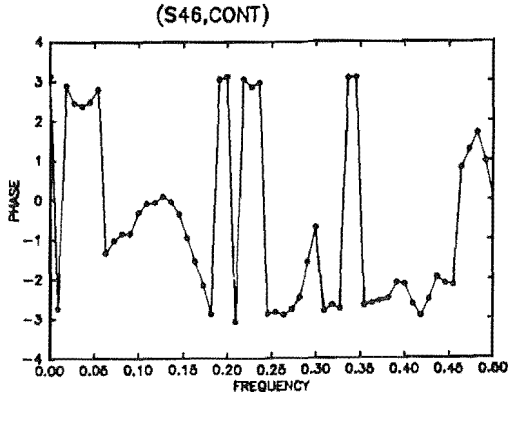

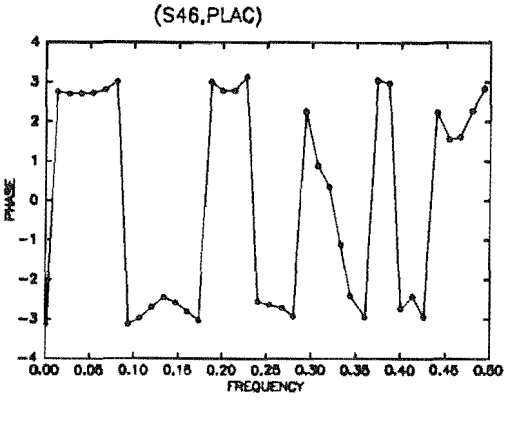

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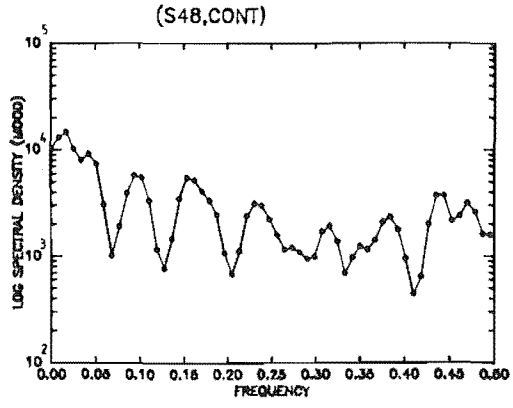

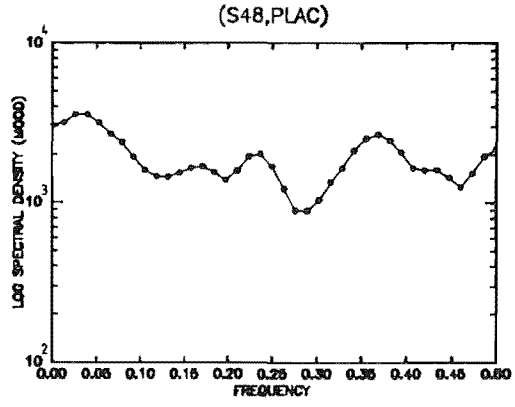

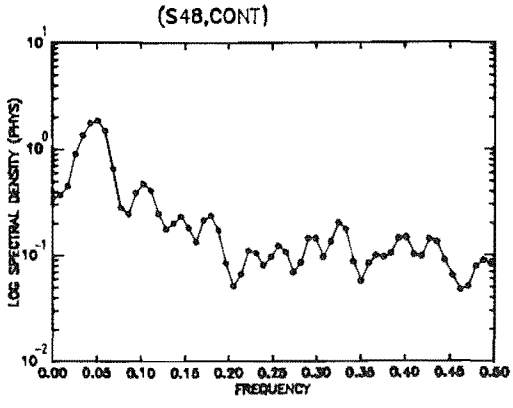

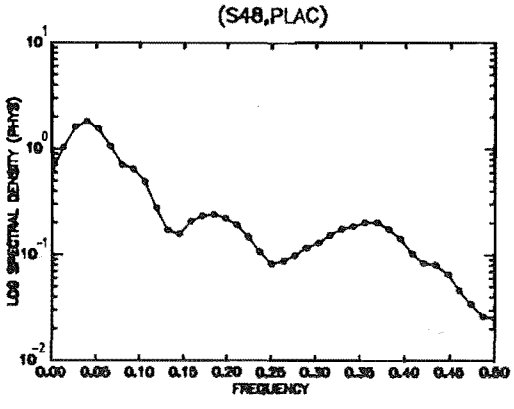

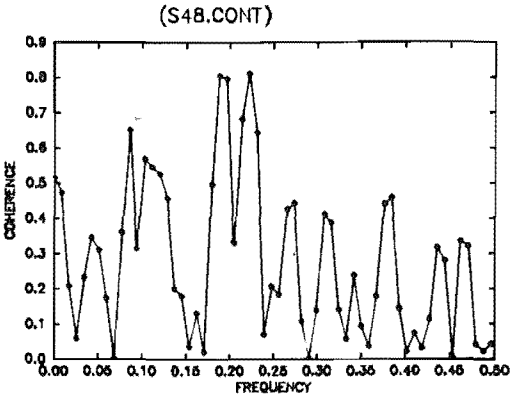

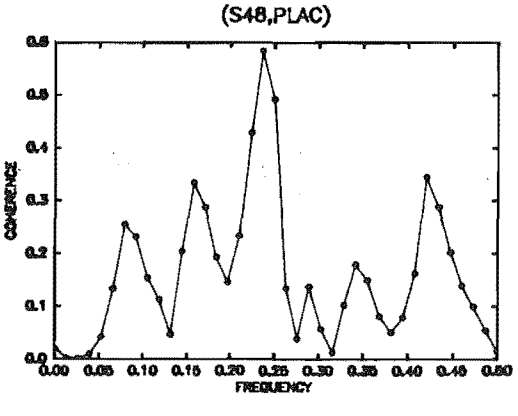

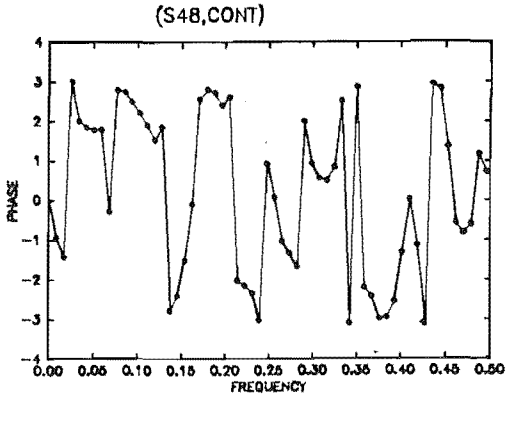

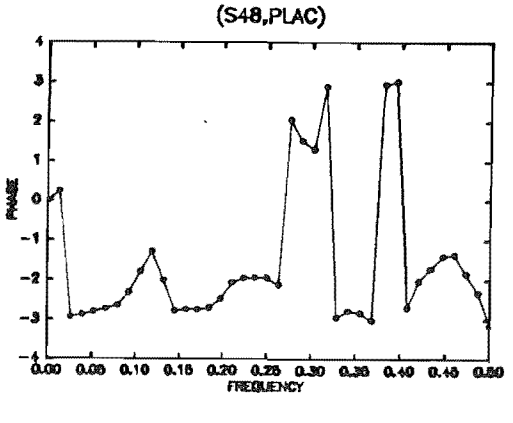

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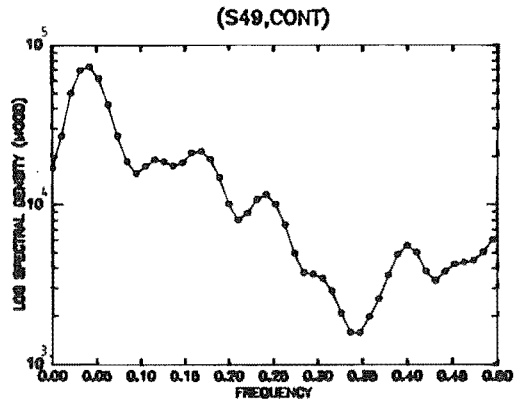

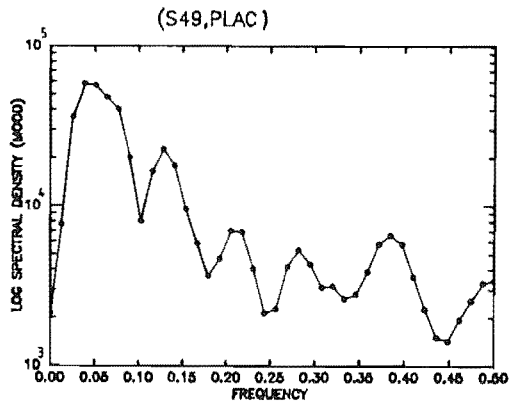

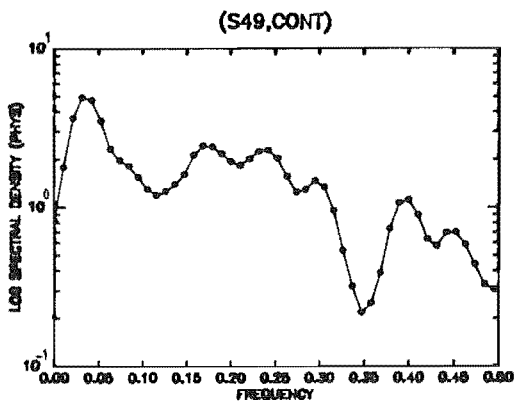

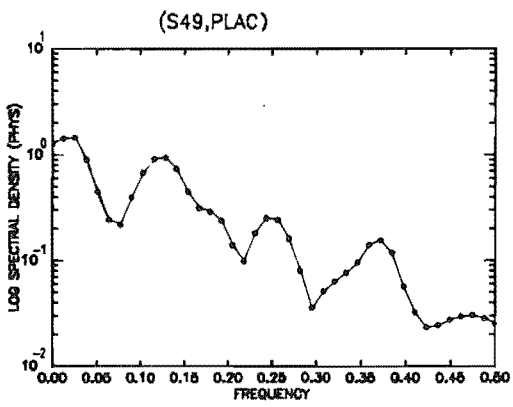

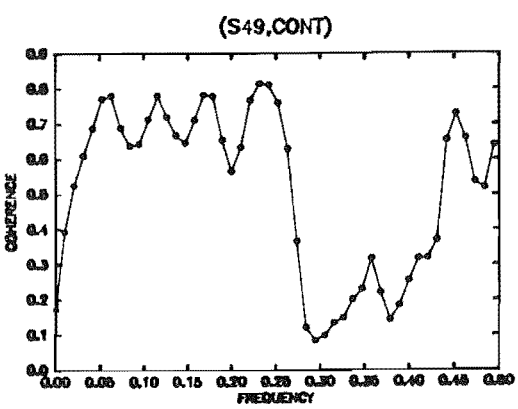

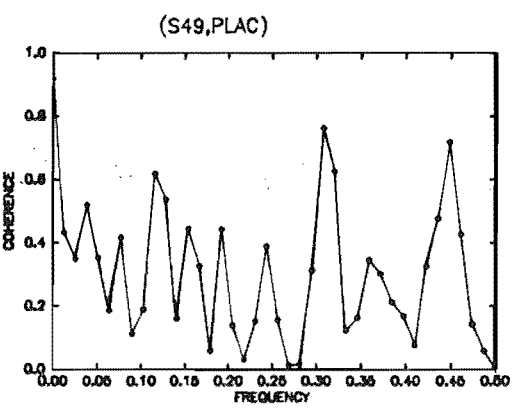

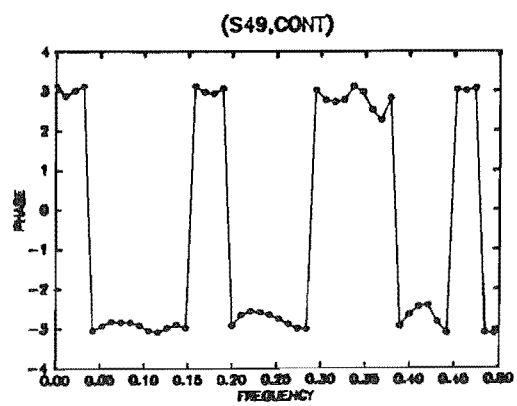

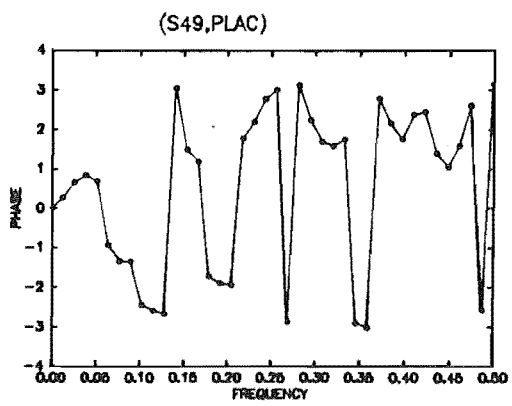

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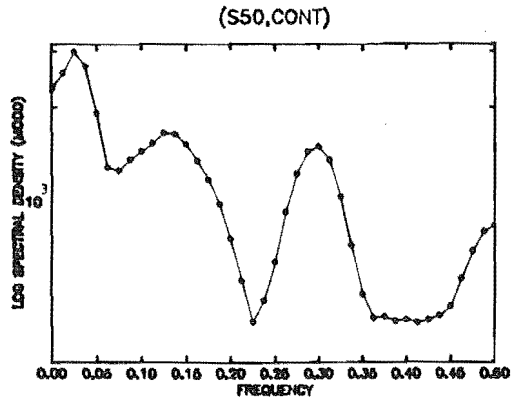

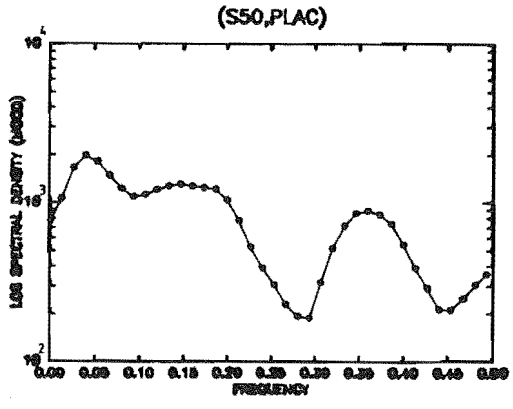

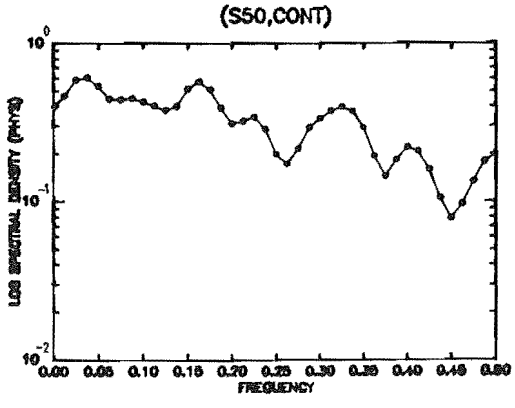

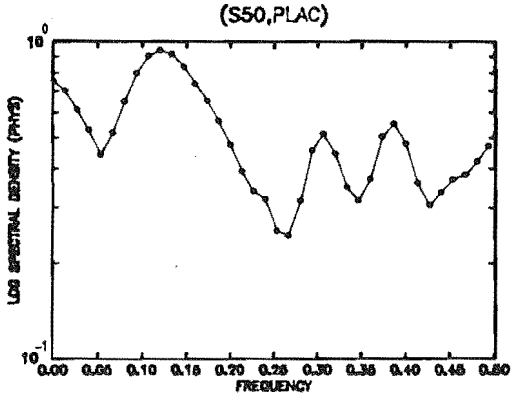

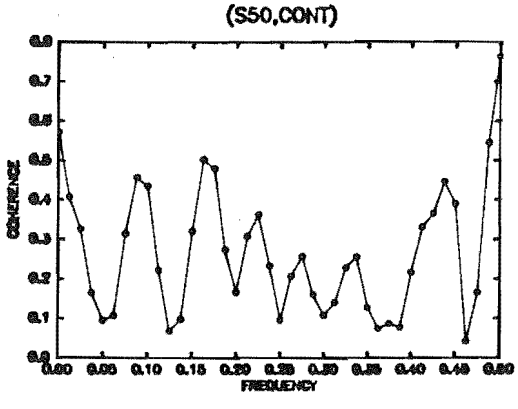

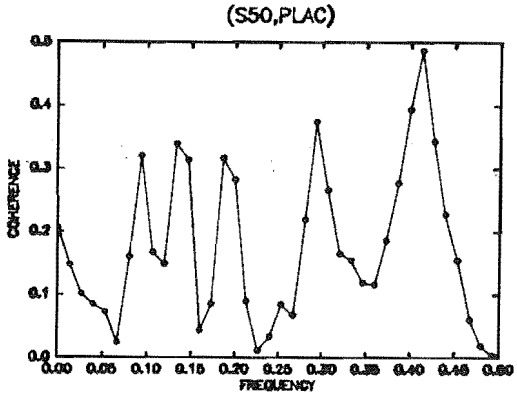

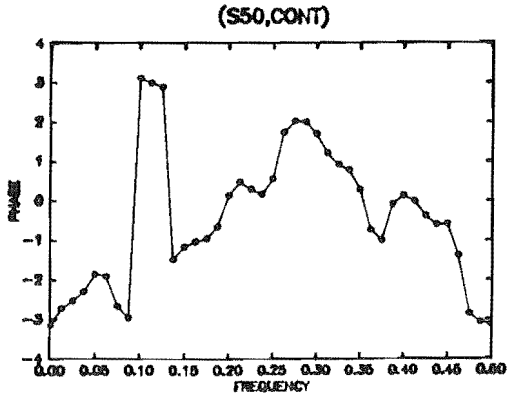

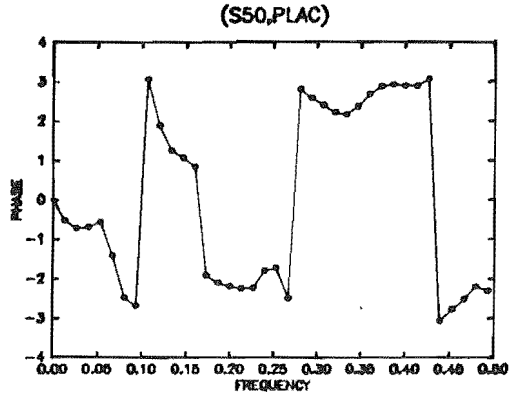

Appendix 7 - Consent Form

PRINCESS MARGARET HOSPITAL

TREATMENT TRIAL - PATIENT CONSENT FORM

PROJECT TITLE:

Investigation of the Premenstrual Tension Syndrome

INVESTIGATORS: *Dr M.G. Metcalf and colleagues*

AIM OF TRIAL OF NEW TREATMENT OR INVESTIGATION

To test a modified treatment for premenstrual tension.

DESCRIPTION OF NATURE AND DURATION OF PATIENT'S INVOLVEMENT:

During 3 menstrual cycles:

1. *to take a daily dose of pyridoxine in glucose*
2. *to keep a daily record of symptoms*
3. *to collect a weekly specimen of urine*

DESCRIPTION OF INCONVENIENCES OR HAZARDS WHICH MIGHT BE EXPECTED:

Nil

STATEMENT BY PATIENT:

I have read the above and have had the opportunity for discussion. I understand that the procedures have been approved by a special hospital committee and that I may withdraw my agreement at any time. I understand that the treatment or investigation will be discontinued immediately if any harmful effects appear. I agree to take part in this study or trial of treatment.

_____ _____

Signature of Patient Date

_____ _____

Signature of Investigator Date